



AMERICAN UNIVERSITY OF BEIRUT

ASSESSMENT AND MANAGEMENT OF ORAL MUCOSITIS: A  
HOSPITAL PROTOCOL

by  
GHINA ABDELKARIM AL ARAB

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submitted in partial fulfillment of the requirements  
for the degree of Master of Science in Nursing Adult Care Track  
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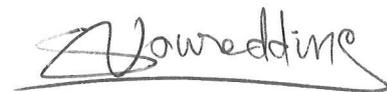
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# AN ABSTRACT OF THE PROJECT OF

Ghina AbdelKarim Al Arab for Master of Science  
Major: Nursing Science Adult Care Track

Title: Assessment and Management of Oral Mucositis: A Hospital Protocol

Oral mucositis is a common side effect of all cancer treatments including antineoplastic drugs, radiation therapy, and bone marrow transplantation, among others with high prevalence. Its impact on the population is linked with severe pain, decreased oral intake, delay in treatment, increased hospital stay, increased cost, decrease in the efficacy of treatment and decreased survival rate. The purpose of this project was to review the available literature on the assessment and treatment of oral mucositis and develop a protocol that can be followed with patients admitted to the American University of Beirut Medical Center who are undergoing cancer treatment.

A thorough search was performed through the databases Academic Search Complete, MedLine and CINAHL to find protocols used to assess and treat oral mucositis in cancer patients and research studies on the topic. The key terms used for this search were: “oral mucositis”, “protocol”, “guideline”, “cancer”, and “cancer patients”. All articles presenting methods for prophylaxis against, prevention or management of oral mucositis were included. Articles were excluded if they addressed other muscositis such as GI mucositis.

Two main guidelines identified were developed by the Oncology Nursing Society in 2009 and the Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology, last updated in 2014. Moreover a few recent studies were found. Many of the recommendations are not based on the strongest level of evidence, due to the lack of randomized trials and inconsistent results of studies. Based on the literature, the protocol developed involved an assessment tool to identify the stage of oral mucositis, and a treatment algorithm targeting each stage. A documentation of form for the protocol was also prepared. Plans for protocol implementation and evaluation plan for the protocol are proposed. The role of the advanced practice nurse in implementation and monitoring protocol use is highlighted.

Oral mucositis is a significant problem in oncology patients. Using evidence based protocol to prevent and manage oral mucositis, nurses can protect their patients from suffering and complications related to this problem.

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# CHAPTER I

## INTRODUCTION

Prevalence of cancer, which is one of the leading causes of death worldwide, is on the rise with breast and prostate cancer occupying the highest prevalence (Meade, 2013). In Lebanon, breast cancer has the highest prevalence at 33.4% in Lebanese females, and bladder cancer at 18.5%; and prostate cancer prevalence of 14.2% in Lebanese males (Shamseddine, 2014). Regardless of the type of malignant tumor, research is often focused on its treatment and its complications. Among the many complications of cancer treatment, oral mucositis is among the most commonly encountered ones. Many trials have addressed this problem in an attempt to treat it, decrease its severity and where possible avoid it (Bhatt et al., 2010; Lalla et al., 2009; Ottaviani et al., 2013; Peterson et al., 2010). However, to our knowledge, there is no one complete evidence based protocol that addresses this problem in a comprehensive manner or informs practice to guide health care providers in caring for patients. To date and based on literature review there is no treatment capable of treating or preventing oral mucositis efficiently. Therefore, this project provides an overview of the current literature on this topic and proposes an evidence based protocol for the prevention and management of oral mucositis. The important aspect of the protocol is the nursing assessment and management initiation of oral mucositis prevention and treatment based on its grade.

### **A. Background**

Oral mucositis is a common side effect of all cancer treatments including antineoplastic drugs, radiation therapy, and bone marrow transplantation, among others (Lalla et al., 2008; Parker, 2005; Peterson et al, 2010). Oral mucositis is an inflammation or

ulceration of the mouth mucosa, which is usually co-existent with formation of a pseudomembrane; the mucosal injury expands across the oral and gastrointestinal mucosa, from the mouth to the anus (Lalla et al., 2008; Peterson et al., 2010). This occurrence is due to the rapid growth and turnover rate of the mucosal cells in the oral cavity, making it more sensitive to chemotherapy and radiotherapy (Jaroneski, 2006; Sieracki et al., 2009). The incidence of this complication ranges between 40% and 80% with patients receiving chemotherapy, where this variance is based on the type and the dosage of the treatment, with high rates of occurrence when methotrexate and 5-fluorouracil (5-FU) are used (Farrington et al., 2013; Peterson et al., 2010; Sieracki et al., 2009). Inpatients receiving radiotherapy, the incidence of mucositis is up to 66% (Meade, 2013). Radiation-induced mucositis begins at cumulative doses of about 15Gy and at 30 Gy it reaches its severe state (Brasil et al., 2012). Based on the World Health Organization (WHO) statistics, the incidence of grade 3 and 4 mucositis is 75% in patients having bone marrow transplant (Peterson et al., 2010).

Oral mucositis can occur as early as four to seven days after initiation of cancer treatment and peaks in its severity within two weeks (Brasil et al., 2012). This complication of cancer treatment can lead to fatal consequences if infection of this membrane occurs (Farrington et al., 2013; Ottaviani et al., 2013; Peterson et al., 2010). The progress of mucositis and its severity are related to several factors pertaining to the patient and the therapy. The patient-related factors include age, type of cancer, poor oral hygiene and tobacco use. Treatment-related factors include type of treatment, dose of chemotherapy or radiotherapy dose fraction, and combination of both treatments. Other factors are the existence of other co-morbidities, such as diabetes mellitus, which may produce further risk of developing oral mucositis (Brasil et al., 2012). Mucositis has the potential to interfere with each aspect of a patient's life and affect his/her quality of life. Possible consequences of oral mucositis are: 1) Increased risk of infection: septicemia, pulmonary infections; 2) Increased

patient discomfort: depression, anxiety, nervousness; 3) Nutritional problems including pain, difficulty in swallowing, dry mouth, change in taste, bleeding, until anorexia and physical deterioration; 4) Increased hospital days and costs; and 5) Delayed treatment or dose reduction that can or may impact the efficacy of treatment and affect patient survival outcome ( Farrington et al., 2013; Merigo et al., 2012).

## **B. Significance**

Oral mucositis is a clinical problem facing all oncology patients receiving treatment in Lebanon with no published studies on its incidence. Based on anecdotal evidence gathered through my experience in the adult oncology unit, I noticed many patients suffering from this problem and a lack of nurses' knowledge on its proper assessment, documentation and preventive measures. Moreover, there is no protocol for the assessment or management of this problem at the American University of Beirut Medical Center (AUBMC). There is a substantial turnover rate of nurses in the oncology inpatient unit, with many having less than five years of experience and having to recruit yearly new nurses, who are mostly fresh graduates with very limited oncology experience. Considering that oncology patients are already vulnerable as a result of their illness, its psychosocial sequelae and side effects of its treatment, it is important to prevent and manage oral mucositis, in order to ensure patients' nutrition and comfort, and reduce the severity and complications associated with oral mucositis. Having a clinical protocol about the management of oral mucositis can be a guide for nurses to use at AUBMC. The objectives of this project are to:

1. Review the available literature on the assessment and treatment of oral mucositis
2. Develop a protocol that can be followed with patients admitted to AUBMC who are undergoing cancer treatment.
3. Propose an implementation and evaluation plan for the protocol

## CHAPTER II

### LITERATURE REVIEW

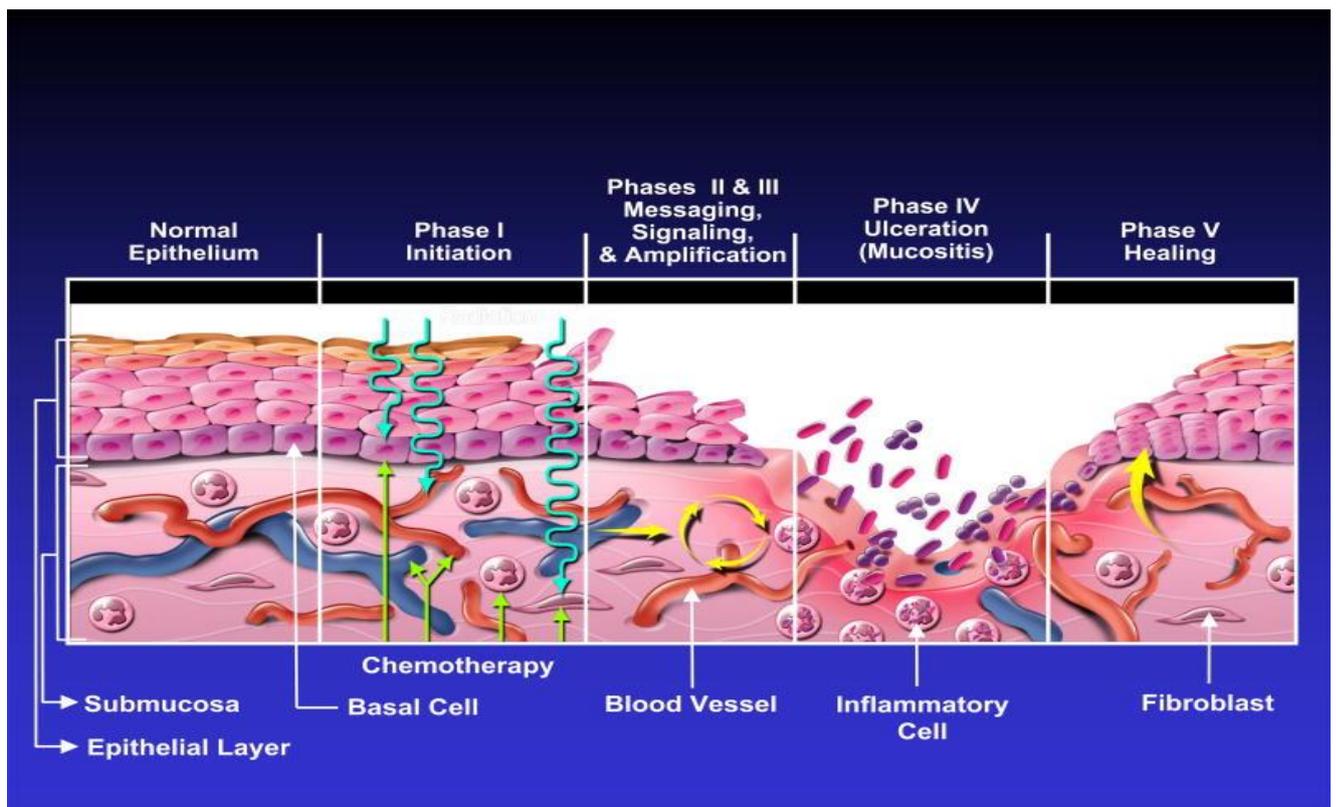
The exact pathophysiology of mucositis is not fully understood, but it is believed to have two mechanisms; direct mucositis and indirect mucositis. The epithelial cells of the oral mucosa undergo rapid turnover, which makes them vulnerable to the effect of cytotoxic therapy. Treatments of cancer cannot differentiate between healthy cells and cancer cells, thus both are injured. In-addition, chemotherapy and radiotherapy can interfere with epithelial cell growth, causing changes to the normal turnover, leading to cell death since they target fast dividing cells, arresting one or more stages of the cell cycle (Sieracki et al., 2009; Silverman, 2007). Oral mucositis can also occur indirectly through the invasion of Gram negative bacteria and fungi, which usually happens in neutropenic patients (Ottaviani et al., 2013).

The mechanism of mucositis development involves five phases as described below (Lalla et al., 2008):

- Phase 1: Initial inflammation. The initiation of tissue injury by radiation and /or chemotherapy induces the release of pro-inflammatory cytokines. These inflammatory mediators increase vascular permeability, thus enhancing cytotoxic drug uptake into the oral mucosa, causing further damage.
- Phase 2: Epithelial phase. In this phase, chemotherapy and radiotherapy prevent oral mucosal epithelial cell division, leading to reduced cells' renewal and increasing their breakdown, resulting in erythema that affects daily activities like swallowing and speech.

- Phase 3: Signaling and amplification. In this phase, up regulation of pro inflammatory cytokines such as tumor necrosis factor- alpha (TNF- $\alpha$ ), produced mainly by macrophages, causes injury to mucosal cells, and also activates molecular pathways that amplify mucosal injury.
- Phase 4: Ulcerative phase. In this phase, there is loss of epithelium that leads to the formation of pseudomembranes and ulcers. Microbial colonization of damaged mucosal surfaces by Gram negative organisms and yeast occurs.
- Phase 5: Healing phase. This phase is characterized by epithelial proliferation as well as cellular and tissue differentiation, restoring the epithelium layer. The figure below shows the five phases.

**Figure 2.1: Pathobiology of Mucositis: A five – Stage process**



Source: Current five phase pathobiologic model of oral mucositis (2004). *Journal of Supportive Oncology*, 2,21-32.

#### A. Assessment of Oral Mucositis

Early detection of oral mucositis is necessary for effective treatment. Various methods of assessment have been described. These assessments are based on the presence of erythema, lesions, pain and difficulty in swallowing. The assessment should include eight sites of the mouth, including the upper labial mucosa, lower labial mucosa, right buccal mucosa, left buccal mucosa, right lateral and ventral tongue, floor of the mouth and soft and hard palate (Jaroneski, 2006; Lalla et al., 2008; Sieracki et al., 2009; Velez, 2004). The WHO has identified four grades of mucositis that depict the degree of severity of the condition:

- Grade 0: indicates absence of mucositis.
- Grade 1: Mild mucositis: localized changes in tissue, patchy erythema, but no feeding problems.
- Grade 2: Moderate mucositis: localized tissue changes, erythema, thinning of the mucosa, small ulcers, mild pain, and difficulty swallowing solid food.
- Grade 3: Severe mucositis: moderate changes in tissue, diffuse erythema and ulcers, bleeding, moderate pain, difficulty with solid and liquid food swallowing.
- Grade 4: Life threatening mucositis: marked changes in tissue, erythema and ulcers involving almost the entire mucosa, bleeding, spontaneous and severe pain, inability to feed. The WHO scale is simple, easy to use scale thus suitable for daily use in clinical practice (Lalla et al., 2008; Merigo et al., 2011; Peterson et al., 2010; Silverman, 2007). The table and figure below show the grading criteria proposed by WHO.

**Table 2.1. WHO Oral Mucositis Grading Scale**

<b>Grade</b>	<b>Description</b>
<b>0 (none)</b>	None
<b>I (mild)</b>	Oral soreness, erythema
<b>II (moderate)</b>	Oral erythema, ulcers, solid diet tolerated
<b>III (severe)</b>	Oral ulcers, liquid diet only
<b>IV (life-threatening)</b>	Oral alimentation impossible

**Figure 2.2. WHO Oral Mucositis Grading Scale**



Source: WHO: [http://www.who.int/en/WHO Handbook 1979, pp.15-22.Sonis et al. \(2004\) Cancer, 100\(9 Suppl\), 1995-2025](http://www.who.int/en/WHO Handbook 1979, pp.15-22.Sonis et al. (2004) Cancer, 100(9 Suppl), 1995-2025).

Another system for grading oral mucositis was developed by the National Cancer Institute, namely the National Cancer Institute Common Toxicity Criteria (NCI-CTC). The NCI-CTC grading scale for mucositis was utilized to assess the severity of mucositis. Grading is from 0-4, where grade 0 means there are no signs and symptoms (no stomatitis); grade 1: Painless ulcers, erythema, or mild soreness in the absence of lesions; grade 2: painful erythema, edema, or ulcers, but the patient can eat or swallow; grade 3: painful erythema, edema, or ulcers requiring intravenous hydration, parenteral or enteral nutritional support; and grade 4: severe ulceration or patient requires prophylactic

intubation (Bhatt et al., 2010; Jaroneski, 2006; Lalla et al., 2008; Ottaviani et al., 2013; Silverman, 2007). This grading scale is characterized by the simplicity of its use and clear criteria for determining the severity of mucositis (Bhatt et al., 2010). The pain dimension of oral mucositis is included in this scale. The strong points of this scale are that mean pain scores correlate with mean scores for dysphagia and stomatitis. Cella et al. (2003) reported that the mean pain scores were significantly correlated with the average scores of oral mucositis and dysphagia. In another study, 77% of the patients reported peak mouth pain within one week of peak dysphagia and stomatitis.(Jaroneski, 2006).The table below shows the National Cancer Institute’s Common Toxicity Criteria (CTC) that were originally developed to aid in the recognition and grading severity of adverse effects caused by chemotherapy treatments.

**Table 2.2. National Cancer Institute’s CTC grading scale for adverse effects caused by chemotherapy**

<b>Grade</b>	<b>Description</b>
<b>Grade 0 (none)</b>	None
<b>Grade 1 (mild)</b>	Painless ulcers, erythema, or mild soreness in the absence of lesions
<b>Grade 2 (moderate)</b>	Painful erythema, edema, or ulcers but eating or swallowing possible
<b>Grade 3 (severe)</b>	Painful erythema, edema, or ulcers requiring IV hydration
<b>Grade 4 (life-threatening)</b>	Severe ulceration or requiring parenteral or enteral nutritional support or prophylactic intubation

Source : NCI-CTC v 2.0, 1999 : <http://ctep.cancer.gov/>Sonis et al.( 2004).*Cancer,1009*(Suppl):1995-2025.

Another scale used in clinical practice is the Oral Mucositis Assessment Scale (OMAS). The OMAS is a commonly used scale to assess mucositis induced by chemotherapy

and radiation therapy. It consists of nine items and allows assessing the site and size of the ulcer, in addition to the severity of erythema. The size is scored from 0 to 3. Zero indicates no ulcer. If the size is  $<1\text{cm}^2$ , the score is 1; if between  $1\text{-}2\text{cm}^2$ , then the score is 2; if  $> 3\text{cm}^2$  then the score is 3. The severity of erythema is scored from 0 to 2. Zero indicates no erythema; 1 for non-severe; and 2 indicates severe erythema (Jaroneski, 2006). This scale is an objective scale, suitable for research purposes; it measures erythema and ulceration at nine different sites in the oral cavity. Sonis and colleagues (1999) tested the psychometric properties of this scale in patients receiving chemotherapy ( $n=108$ ) or radiation ( $n = 56$ ) in a multicenter trial with two observers doing the measurements independently. High inter-observer reproducibility was noted through strong correlations (correlation coefficient  $r > 0.92$  for the three highest scores over the course of assessment, and  $r > 0.83$  for individual sites). All correlations were highly significant at  $P < 0.001$  (Sonis et al., 1999). The strong points of this scale are that scores are strongly correlated with symptoms associated with oral mucositis. The scale is effective at tracking mucosal changes over time; is easy to use, taking less than five minutes to perform; and includes pain aspect of oral mucositis (Jaroneski, 2006). Yet measuring the size may be cumbersome in daily practice. Tables 3 and 4 show the grades of the OMAS.

**Table 2.3. The Oral Mucositis Assessment Scale (OMAS) System: Erythema**

<b>Score</b>	<b>Description</b>
<b>0</b>	None (no change in the color of the mucosa)
<b>1</b>	Mild/moderate (increase in the intensity of the color of the mucosa)
<b>2</b>	Severe (mucosa the color of fresh blood)

**Table 2.4: Ulceration/pseudomembrane Formation**

<b>Score</b>	<b>Description</b>
<b>0</b>	No lesions
<b>1</b>	Cumulative surface area of lesion(s) in a single site less than 1 cm <sup>2</sup>
<b>2</b>	Cumulative surface area of lesion(s) in a single site greater than or equal to 1 cm <sup>2</sup> and less than or equal to 3cm <sup>2</sup>
<b>3</b>	Cumulative surface area of lesion(s) in a single site greater than 3 cm <sup>2</sup>

Source: Sonis, Oster, Fuchs, et al. (2001) *Journal of Clinical Oncology*, 19, 2201-2205.

In conclusion, the most commonly used assessment scales for oral mucositis are the WHO, NCI - CTC and OMAS scales. All of them include a description of the extent of erythema, presence of pain and ulceration. The WHO and the NCI-CTC scales address subjective and objective parameters (redness, pain and ulceration), in addition to functional outcomes (ability to eat) to arrive to one score that reflects the severity of the condition. On the other hand, the OMAS produces two scores; one for ulceration and one for erythema without functional findings. Yet it requires measuring the size of the lesions. The ideal and most suitable assessment scale has to precisely reflect objective and subjective clinical changes and at the same time be easy to teach and use in clinical practice, so that proper management can be instituted accordingly.

### **B. Treatment of Oral Mucositis**

A number of treatment modalities are available for oral mucositis: Laser therapy, cryotherapy, growth factors, analgesics, mouth washes, administration of antimicrobial agents, vitamins and anti-inflammatory agents. Laser therapy is the use of low-level laser therapy that may reduce the levels of reactive oxygen species and/or pro-inflammatory cytokines that contribute to the pathogenesis of mucositis. Cryotherapy or oral cooling is the administration of ice chips to the oral cavity during administration of chemotherapy, which

results in decreased delivery of the chemotherapeutic agent to the oral mucosa, through local vasoconstriction and reduced blood flow. Growth factors are thought to promote epithelial cell proliferation in the management of oral mucositis. Analgesics are used to reduce pain resulting from oral mucositis. Mouth washes include oral rinses used to decontaminate the oral cavity, thus reducing the severity of oral mucositis. Moreover, antimicrobial agents are used to prevent and treat infections known to exacerbate mucositis. Anti-inflammatory agents and vitamins are used to reduce the injury associated with the inflammatory process and nutritional deficiencies, respectively(Bhatt et al., 2010; Dauncey et al., 2012; Farrington et al., 2013; Harris et al., 2008; Lalla et al., 2009; Ottaviani et al., 2013;Sieracki et al., 2009;Yarom et al., 2013).

The Oncology Nursing Society (ONS) has worked with a number of members to create the “Putting Evidence into Practice” (PEP) resource, where the recommendations are based on the latest research evidence. The PEP work on mucositis was posted on the ONS website on 2009 where interventions have been applied based on Weight of Evidence Classification Schema. Clinical Journal of Oncology Nursing (CJON) 2009 article – Putting Evidence into Practice: Evidence – Based Interventions for the Management of Oral Mucositis). The table below shows the grading system for the recommendations by the ONS.

**Table 2.5. Putting Evidence into Practice Weight –of-Evidence Classification Schema**

<b>Weight-of-Evidence Category</b>	<b>Description</b>
<b>Recommended for practice</b>	Effectiveness is demonstrated by strong evidence from meta analysis or systematic reviews. At least two multisite, well-conducted randomized controlled trials (RCT) with at least 100 subjects.
<b>Likely to be effective</b>	Evidence is less than that in Recommended for practice where it is based on one well conducted RCT.
<b>Benefits balanced with harms</b>	Beneficial and harmful effects are weighed based on individual condition and priorities.
<b>Effectiveness not established</b>	Data are insufficient, or there is conflicting evidence
<b>Effectiveness unlikely</b>	No benefit and unacceptable toxicities found in observational or experimental studies
<b>Not recommended for practice</b>	Harm is demonstrated or cost exceeds benefit

Source: ONS (2009). Putting Evidence into Practice: Evidence – Based Interventions for the Management of Oral Mucositis. Clinical Journal of Oncology Nursing.

Recommendations for management by the ONS (2009) are thus categorized based on the identified classes of evidence as described above. The section below presents those recommendations, with additional recent evidence as available.

***1. Recommended for practice***

- **Oral care:** Oral care helps to minimize the effects of oral mucositis in patients receiving treatment by reducing microbial flora, thus preventing infection. The oral care protocol includes assessment, patient education, tooth brushing, flossing, and the use of oral rinses such as normal saline rinses and sodium bicarbonate (Harris et al., 2008).
- **Cryotherapy:** The rationale for the use of cryotherapy is based on the theory that the cold-induced vasoconstriction decreases exposure of the oral mucosa to the cytotoxic

agents administered. The patient sucks on ice chips or drinks ice cold water when receiving 5- Fluorouracil (5-FU) , high dose Melphalan and chemotherapy with short half-life (Brasil et al.,2012; Lalla et al., 2008; Peterson et al., 2010). Use of cryotherapy for bolus 5- FU is supported in the Multinational Association of Supportive Care in Cancer MASCC (2005) guidelines, which were issued by the Basic Oral Care Group subcommittee that reviewed 32 relevant studies and developed a set of recommendations on the prevention and treatment of oral mucositis. Two randomized trials demonstrated 50% reduction in mucositis upon using cryotherapy in patients receiving 5- FU chemotherapy bolus (cited in Stokman et al., 2006). Specifically one study found that mucositis was significantly reduced by cryotherapy considering both the first cycle of therapy (the mean toxicity score for the cryotherapy group was 0.59 vs. 1.1 for the control group,  $P<0.05$ ), and for all the chemotherapeutic courses (the mean toxicity score for cryotherapy was 0.36 vs. 0.69 for the control group,  $P<0.05$  (Cascinu, Fedeli, Fedeli& Catalano, 1994).A recently published systematic review of the use of cryotherapy for managing oral mucositis included studies done after 2008 (Peterson et al., 2013). The authors concluded that results of the studies consistently showed a significant benefit for cryotherapy although their rigor varied. So they recommended maintaining the recommendation to use cryotherapy to prevent oral mucositis in patients receiving 5-FU and suggesting its use in patients receiving Melphalan (Peterson et al., 2013).

## ***2. Effectiveness Not Established***

Agents examined in the review of literature were assigned to this category because of lack of clinical trials or inadequate sample size in the reviewed studies.

- **Antimicrobial agents:** Antimicrobial agents include polymyxin, tobramycin, amphotericin B and fluconazole. Based on the literature, those medications have no clear benefit and little evidence exists about their benefit (Stokman et al., 2006).
- **Growth factors and cytokines:** Granulocyte- colony- stimulating factor and granulocyte macrophage – colony stimulating factor (GM-CSF) promote neutrophil development in the submucosa. In a meta-analysis, Stokman and colleagues (2006) reviewed 13 randomized placebo-controlled trials that tested the effect of GM-CSF and G-CSF with systemic administration or local application by mouthwashes, during cancer treatment via chemotherapy or radiotherapy, or both. Six studies used GMCSF/G-CSF for systemic administration, and four studies used GM-CSF/G-CSF as a mouth wash. The investigators found a significant effect of GM-CSF and G-CSF in preventing mucositis in the systemic intervention group, with an odds ratio (OR) of 0.53 (Confidence interval [CI] 0.33-0.87). No preventive effect was found for the topical administration of GM-CSF and G-CSF; OR = 0.32 (CI: 0.06-1.67) (Stokman et al., 2006).

A randomized double blind placebo controlled study reported by the same investigators was done to check the effect of recombinant human keratinocyte growth factor (rhuKGF) Palifermin. The findings showed that IV Palifermin significantly reduced the incidence of mucositis (by 35%) and the duration of severe mucositis by 3 days in patients undergoing total body irradiation pre Bone Marrow Transplant. (Spielberger et al., 2004, cited in Stokman, et al, 2006).

- **Allopurinol:** It inhibits the toxic enzymes that are produced by 5FU. Initial small trials found some good results using allopurinol mouthwash; yet those results were not confirmed in controlled trials (Yarom et al., 2013)

- **Low level laser therapy** is suggested to reduce pain associated with chemotherapy, radiotherapy or both. However, this treatment requires high technology and training (Peterson et al., 2010). A recent study done by Ottaviani et al. (2013) on the effect of a 4-day treatment with laser therapy on 20 patients with chemotherapy-induced mucositis treatment showed the following: all patients tolerated low power laser therapy with no adverse events and complete recovery in swallowing and chewing was achieved after treatment ( $P < 0.05$ ). Oral lesions healed completely 3 weeks following therapy in 70% of patients (Ottaviani et al., 2013).
- **Multi- agent (magic or miracle) oral rinses:** These include Lidocaine, Diphenhydramine, and Maalox. These agents are swished and expectorated; they are widely used, and there is no formal testing of such combination. In addition, diphenhydramine is a sedating agent and may cause unpleasant difficulty in swallowing (Brasil et al., 2012).
- **Coating agents:** An example is Caphosol, which is a Food and Drug Administration (FDA) approved rinse composed of sodium chloride, sodium phosphate and calcium chloride that showed effectiveness in pain management and decreased symptoms of xerostomia in patients undergoing bone marrow transplant (Brasil et al., 2012).

### ***3. Not recommended for practice***

**Chlorhexidine:** This antiseptic solution was the traditional used mouthwash; however, recent studies found that it causes negative effects; such as bitter taste and dental pigmentation (Stokman et al., 2006).

### ***4. Expert opinion***

**Bland rinses:** those include 0.9% saline (normal saline), sodium bicarbonate, and a saline and sodium bicarbonate mixture. Sodium bicarbonate was found to dilute the accumulated mucus and decrease yeast colonization (Harris et al., 2008).

Another set of guidelines for the management of oral mucositis was proposed by the European Nursing Society (EONS) based on those developed by Multinational Association of Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) that were developed in 2004 and revised in 2005. The EONS recommended the use of the WHO criteria for assessing the oral mucositis. The treatment recommendations were updated in 2014. The levels of evidence used go from 1 to 5, with 1 designating meta-analysis of well designed randomized or controlled trials and 5 for evidence from case reports and clinical expertise (MASCC/ISOO, 2014). Recommendations for prevention of oral mucositis include:

- 1- Oral cryotherapy for 30 minutes prior to bolus 5-FU chemotherapy (level of evidence [LOE] 2). Oral cryotherapy is suggested in patients receiving high dose of chemotherapy (Melphalan) combined with or without total body irradiation as conditioning for hematopoietic stem cell transplantation (LOE 3).
- 2- Recombinant Keratinocyte Growth Factor-1 (KGF/palifermin) at 60 µg/kg/day for 3 days prior to conditioning treatment or for a hematologic malignancy it is suggested to be given 3 days post-transplant in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation (LOE 2).
- 3- Low level laser therapy (wavelength at 650nm, power of 40mW, and each cm<sup>2</sup> treated with the required time to a tissue energy dose of 2 J/cm<sup>2</sup>) in patients receiving hematopoietic stem cell (HCT) transplantation conditioned with high dose chemotherapy, or with total body irradiation (LOE2). The guidelines suggest low level laser therapy (wavelength ~ 632.8 nm) in patient undergoing radiotherapy without chemotherapy for head and neck cancer (LOE 3).
- 4- Benzylamine mouthwash in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy) without chemotherapy (LOE 1).

- 5- Zinc oral supplements in oral cancer patients receiving radiotherapy or chemotherapy is suggested (LOE 3)
- 6- Oral care protocols in all age groups and across all cancer treatment modalities are suggested (LOE 3).

On the other hand, the guidelines recommend against using the following: PTA (Polymyxin, Tobramycin and amphotericin B) and BCoG (bacitracin, clotrimazole and gentamicin) to prevent mucositis in patients receiving radiation therapy for head and cancer(LOE 2); GM-CSF in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplant(LOE 2); iseganan antimicrobial mouthwash or systemic pilocarpine administered orally in patients receiving high dose chemotherapy with or without total body irradiation, for HCT(LOE 2); also Sucralfate mouthwash in patients receiving radiotherapy (LOE 2) and chemotherapy (LOE 1) for head and neck cancer; or IV glutamine in patients receiving high dose chemotherapy with or without total body irradiation for HCT (LOE 2). Weaker evidence (LOE 3) led to the suggestion against using Chlorhexidine or Misoprostol mouthwash to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer, or systemic pentoxifylline orally in patients undergoing bone marrow transplantation (MASCC/ISOO, 2014)..

Treatment recommendations for oral mucositis include (MASCC/ISOO, 2014):

1. Pain Management using Patient controlled analgesia (PCA) with Morphine to treat oral mucositis pain for patients undergoing hematopoietic stem cell transplantation (LOE 2)
2. Transdermal Fentanyl is suggested for oral mucositis pain resulted in patients who are receiving conventional or high-dose chemotherapy with or without total body irradiation (LOE 3).

3. Mouthwash with 2% Morphine is suggested to treat oral mucositis pain in patients receiving chemotherapy and radiation for treating head and neck cancer (LOE 3).
4. Mouthwash with 0.5% Doxepin may be effective to treat pain (LOE 4).

The only oral mucositis protocol that was published to our knowledge was developed by Bhatt et al. (2010) and pilot tested on patients undergoing HCT. The assessment was done using the CTC scale. The interventions included tooth brushing, cryotherapy, Chlorhexidine, normal saline, magic solution and Caphosol mouth rinses. Also Palfermin was included as treatment in the protocol, at the physician's discretion. The authors did a retrospective review of medical records of patients who underwent HCT over three months before the protocol implementation. Then patients undergoing HCT after protocol implementation were followed up and incidence, duration and severity of mucositis were assessed over three months. There was a trend of reduced incidence of mucositis though not statistically significant ( $p=0.09$ ); only grade 1 mucositis incidence was reduced significantly from 100% to 67% ( $p=0.039$ ). The duration of mucositis was reduced significantly from 19.2 days to 8.3 days ( $p=0.02$ ). In terms of severity, three protocol patients did not develop mucositis (grade zero) whereas all those in the pre-protocol group had some degree of mucositis. Another significant effect included fewer days requiring parenteral nutrition (10.2 vs. 17.4 days,  $p=0.02$ ) in the protocol compared to the control group (Bhatt et al., 2010). It is worth noting that the algorithm does not guide what intervention to use based on the grade and some of its recommendations are outdated (for instance the use of Chlorhexidine).

Oral mucositis is a clinical significant problem that affects the wellbeing of patients. Therefore it is so important to accurately diagnose oral mucositis and initiate preventive and treatment measures to reduce undesirable outcomes. Although in the literature there are several recommendations and therapeutic approaches for prevention and treatment, no single

agent was found to be totally effective. Significant recommendations emphasize controlling the severity of mucositis by proper assessment and provision of oral hygiene as a standard treatment to prevent and reduce complications. Many recommendations are not based on the highest level of evidence. Thus continued evaluation and trials are needed to come up with a standard protocol that should improve treatment outcomes.

## CHAPTER III

### THE PROPOSED PROTOCOL

Oncology nurses play a crucial role in the care, management and in the outcome of treatment in oncology patients. Following the oral care protocol that will be developed will help them make a new difference in the patient's life. Oncology nurses will assess all patients and initiate the oral mucositis protocol based on the scoring. This chapter describes the protocol and its implementation.

#### **A. Protocol Description**

The protocol is based on the literature and what is available in Lebanon. The protocol is divided into three parts: 1- Assessment 2- Intervention 3- Patient and Family education

##### ***1. Assessment***

Upon admission the nurse will assess the oral mucosa of all adult oncology patients using the AUBMC oral mucositis assessment tool that was developed in 2008. This assessment tool is based on WHO, the Oral Assessment Guide and the National Cancer Institute Common Toxicity Criteria (NCI-CTC) of oral mucositis tools and includes all the criteria mentioned in the tools; it is called the Oral Mucositis Assessment Tool. The table below shows the tool that is currently used at AUBMC.

**Table3.1.The AUBMC oral mucositis assessment tool**

American University of Beirut Medical Center  
Nursing Services  
**ORAL MUCOSITIS ASSESSMENT TOOL**

Grade 0	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade4(Lifethreatening)
<ul style="list-style-type: none"> <li>• no atrophy</li> <li>• no ulcers</li> <li>• no erythema</li> <li>• no edema</li> <li>• no pain (score 0-1)</li> <li>• no salivary changes</li> <li>• no oral mucosal changes</li> <li>• color: pink oral mucosa</li> <li>• no lesions</li> <li>• no bleeding</li> <li>• normal function and appearance of mouth</li> </ul>	<ul style="list-style-type: none"> <li>• painless oral ulcers</li> <li>• erythema of the mucosa</li> <li>• mild oral soreness in the absence of lesions</li> <li>• may experience mild pain (score 1-2), not requiring analgesics</li> <li>• normal function</li> </ul>	<ul style="list-style-type: none"> <li>• painful oral ulcers, edema or erythema</li> <li>• patchy pseudo-membranous reaction (&lt;1.5cm)</li> <li>• patches may produce inflammatory sero-sanguinous discharge</li> <li>• may experience moderate pain (score 3-6)</li> <li>• solid diet tolerated</li> </ul>	<ul style="list-style-type: none"> <li>• painful oral ulcers, edema or erythema</li> <li>• pseudo-membranous reaction (&gt;1.5cm)</li> <li>• may include severe pain requiring narcotics (score 6-9)</li> <li>• liquid diet only tolerated, not able to swallow solid diet</li> <li>• requiring IV hydration</li> </ul>	<ul style="list-style-type: none"> <li>• severe oral ulceration, hemorrhage or necrosis</li> <li>• ulceration and occasional bleeding not induced by minor trauma or abrasion</li> <li>• oral feeding impossible, requiring parenteral nutrition (TPN)</li> <li>• worst pain (score 9-10) requiring narcotics; topical or S/C pain medications or patient controlled analgesia</li> <li>• patient sometimes can take oral (PO) medications but otherwise nil by mouth</li> </ul>

Eight sites in the oral cavity to be evaluated when assessing the oral mucosa:

(1) Upper labial mucosa (upper lip), (2) Lower labial mucosa (lower lip), (3) Right buccal mucosa (right inner cheek), (4) Left buccal mucosa (left inner cheek), (5) Right lateral and ventral tongue, (6) Left lateral and ventral tongue, (7) Floor of the mouth, (8) Soft palate.

AUBMC Oral Mucositis Assessment Tool/MedSurg CPC/ Feb/2008

The assessment done will be documented and the patient result will be categorized into one of five scoring categories:

- A. Grade zero: Standard care for all oncology patients receiving chemotherapy or radiotherapy or both because they are at risk to develop oral mucositis
- B. Grade 1: Patients with mild risk
- C. Grade 2: Patients with moderate risk
- D. Grade 3: Patients with severe risk
- E. Grade 4: Patients with life threatening risk

**2. Intervention**

The interventions will be provided based on the assessment grades.

Patients who score zero will receive standard care, which mostly involves general recommendations for assessment and prevention. These recommendations are:

- Using a flashlight, the nurse will inspect the patient's mouth daily at least once, looking through all the sides of the mouth including the lips for any changes or lacerations.
- The nurse will follow up on the following oral care interventions done by the patient:
  - The patient will brush his/her teeth, tongue and gums with an extra soft toothbrush after each meal and at bed time daily for 90seconds.
  - The patient will floss his/her teeth if platelet counts are more than 50,000/mm<sup>3</sup>. The patient must avoid flossing if his/her gums are painful or bleeding. The patient will rinse the mouth with 15-30 ml of normal saline (ready made from pharmacy) for 30 seconds after flossing or brushing, swish thoroughly and spit out.
- The nurse educates the patient on using the following solution done at home by adding 1/4 teaspoon baking soda and 1/8teaspoon salt mixed in 1 cup of warm water.
- The lips should be kept moist using water based Lubricants or Vaseline Petroleum.
- Do not use solutions that contain alcohol.
- If the patient has dentures the nurse should make sure they fit well and limit how long the patient is wearing them each day. The dentures must be kept clean by brushing them with a separate tooth brush.

Patients with oral mucositis Grade 1 will receive standard care (mentioned above for grade zero). In addition, these patients may swish and spit with sodium bicarbonate instead of normal saline every 4 hours.

Patients with oral mucositis Grade 2 will:

- Receive standard care
- Use magic (or miracle) rinses, which include equal amounts of lidocaine, diphenhydramine, and Maalox (1/3 of each) to swish and spit every 4 hours.

- A dietitian will be consulted for vitamins and dietary supplement adding vitamin A, E and C to his diet.

Management of patients with oral mucositis Grade 3 includes:

- Standard care
- Use of magic (or miracle) rinses, which include equal amounts of Mycostatin, lidocaine, and Maalox (1/3 of each) to swish and spit every 4 hours OR a solution that includes 1/3 Sodium Bicarbonate, 1/3 Lidocaine and 1/3 Maalox to swish and spit every 4 hours OR Glutamine 4 g of powder dissolved in liquid to swish and swallow twice daily OR Nystatin or Mycostatin solution to swish and swallow every 4 hours. These options provide flexibility for patients depending on what is available.
- Consultation of a dietitian for vitamins and dietary supplement adding vitamin A, E and C to his diet.
- Pain management using Morphine subcutaneously or transdermally.

Patients with oral mucositis Grade 4 will receive the following care:

- Using a flashlight, the nurse will inspect the patient's mouth daily at least once (look through all the sides of the mouth including the lips for any changes or laceration).
- A mouthwash containing Zinc to swish and swallow. Alternatively, patients may receive Caphosol mouthwash: 30ml swish for 1 minute with 15ml of the solution and spit out. Repeat with the remaining 15ml of the solution and spit out. Repeat four times daily after normal saline mouthwash.
- Low Level Laser Therapy
- Palifermin 60microgram/kg/day IV Drip 3 days before and 3 days following high doses of chemotherapy.
- Antifungal, antibiotics and antiviral can be added if needed based on assessment by the infections doctors.

- Systemic pain management with IV Morphine.
- Dietary consult and start total parenteral nutrition with vitamin supplement (vitamins A, E, C and folic acid).

In case of bolus with short half life chemotherapy (bolus 5-FU, Melphalan), patients need to use oral cryotherapy prior, during and 30 minutes after treatment.

### ***3. Patient and Family Education***

The nurse will instruct the patients on examination of oral cavity, and provide detailed instructions on brushing and flossing, rinsing the mouth, inspecting and when to seek medical advice. Patients are also instructed to:

- Visit a dentist before cancer treatment starts or at least need to be examined by a dentist as soon as possible after treatment.
- Perform oral assessments daily and document findings.
- Report to the physician when new or worsening of symptoms occurs.
- Avoid tobacco, alcohol and irritating foods (e.g. acidic, hot, rough, spicy, beverages)
- Use water –based moisturizers to protect lips.
- Maintain adequate hydration.

Appendix A shows an algorithm displaying the proposed protocol.

### **B. Protocol Implementation**

The protocol will be shared with the oncology clinical nurse specialist (CNS) for review. Based on feedback of the CNS, final modifications will be made. Then a multidisciplinary task force will be formed to gather feedback from the oncologists, dietary and pharmacy departments. The protocol will be finalized and a proposal sent to the administration for approval. The algorithm depicting the protocol will be posted on the units and sessions planned to educate the staff about the new protocol (see Appendix A). A flow sheet for documenting assessment and treatment will be included in the medical records (see

Appendix B). After all the staff is educated, the new protocol will be pilot tested for 3 months. Feedback will be sought from the staff about the feasibility of its implementation and modifications made accordingly. Then the protocol will be implemented in its final form.

## CHAPTER IV

### EVALUATION AND RECOMMENDATIONS

Like any change in practice, evaluation of the protocol is needed to assess its effectiveness in improving patient outcomes. Based on the pilot test results, final refinements will be made before the main implementation of the protocol is accomplished. A pre-post evaluation study is then planned. Medical records of patients admitted to the adult oncology units will be reviewed for the past year prior to the protocol implementation and the following data will be collected: 1) Incidence of Oral Mucositis; 2) Progress of oral mucositis during hospitalization in patients who develop it; 3) Documentation of Oral mucositis assessment, care and related patient education; 4) Pain scores of patients with documented oral mucositis and analgesics given; in addition to 5) any complications documented such as oral infections, dysphagia, food intake, reduced weight; 6) length of stay; 7) delay in treatment related to oral mucositis; 8) use of analgesics/ narcotics for oral pain; 9) use of antimicrobial agents for oral infections; and 10) hospitalization costs. Then six months following implementation the same data will be collected. The data will be compared. Patients' satisfaction with oral mucositis care and the education provided to them can also be gathered as additional evidence for the effectiveness of and compliance with the protocol. The protocol will be reviewed every five years in light of any new research evidence.

Oral mucositis is a common side effect of cancer treatment. Early detection and treatment are possible with diligent nursing care. The proposed protocol aims to improve the quality of care for oncology patients by providing nurses with evidence based guidelines for the management of this condition and standardizing the care provided. Linking the assessment

findings to the interventions provided can guide the nurses in providing appropriate care for the patients. With evidence based practice, better patient outcomes are expected.

## REFERENCES

- Bhatt, V., Vendrell, N., Nau K, Crumb D, Roy V (2010) Implementation of a standardized protocol for prevention and management of oral mucoitis in patients undergoing hematopoetic cell transplant. *Journal of Oncology Pharmacology practice*, 16, 195-204.
- Brasil, C., Sepra, M., Franca, .T, castro, J. (2012). Management of oral mucositis. *Archives of Oncology*, 19, 57-61
- Cascuni, S., Fedeli, A., Fedeli, S. L., & Catalno, G. (1994). Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. *European Journal of Cancer :B Oral Oncology*, 30B(4), 234-6.
- Cella, D., Pulliam, J., Fuchs, H., Miller, C., Hurd, D., Wingard, J. R. Giles, F. (2003). Evaluation of pain associated with oral mucositis during the acute period after administration of high-dose chemotherapy. *Cancer*, 98(2), 406-412.
- Current five phase pathobiologic model of oral mucositis (2014). *Journal of Supportive Oncology*, 2, 21=32.
- Dauncy, J., Greedy, J., Morgan, K. (2012). Prevention and management of treatment- related oral mucositis. *Head and neck cancer*, 11, 23-28
- Farrington, M., Cullen, L., Dawson, C. (2013). Evidence based oral care for oral mucositis. *Head and neck cancer*, 31, 6-15
- Harris, D., Elires, J., Harriman, A., Cashavelly, B., Maxwell, C. (2008). Putting Evidence Into Practice: Evidence Based Interventions for the Management of Oral Mucositis. *Clinical Journal of Oncology Nursing*, 12, 141-152
- Jaroneski, L. (2006). The Importance of Assessment Rating Scales for Chemotherapy-Induced Oral Mucositis. *Oncology Nursing Forum*, 33, 1085-1092

- Lalla, R., Sonis, S., Peterson, D. (2008), Management of oral mucositis in patients with cancer. *Dental Clinics of North America*,52, 61-77
- MASCC/ISOO Evidence-based clinical practice guidelines for mucositis secondary to cancer therapy. (2013). Retrieved April 3rd, 2014, from <http://www.mascc.org/mucositis-guideline-publications>
- Meade, E. (2013). Cancer–related oral considerations: implications and treatment. *Cancer*, 100(9 Suppl), 2026-2046.
- Mergio, E., Fontana, M.,Fornaini, C., Clini, F., Cella, L., Vescovi, P., Oppici, A. (2012), Preliminary study on radio-chemo-induced oral mucositis and Low Level Laser Therpay. *Advances in Laserology*, 1486, 137-141
- Ottaviani, G., Margherita, G., Sturnega, M., Matine, I. V., Mano, M., Zanconati, F., Bussani, R., Perinetti, G., Long, C., Lenarda, R., Giacca, M., Biasotto, M., and Zacchinga, S. (2013). Effect of Class 4 Laser therapy on Chemotherapy- Induced Oral Mucositis. *The American Journal of Pathology*,183, 1783-1757
- Parker, L. (2005). Prevention and Management of Oral Mucositis for an Outpatient Oncology Setting, *The Oklahoma Nurse\_ June, July, August*, 10-12
- Peterson, D. E., Öhrn, K., Bowen, J., Flidner, M., Lees, J., Loprinzi, C., Mori, T., Osaguona, A., Weikel, D. S., Elad, S., Lalla, R. V. for the mucositis study group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (2013). Systematic Review of oral cryotherapy for management of oral mucositis caused by cancer therapy.*Support Care Cancer*, 21, 327 – 332.
- Peterson, D. E., Bensadoun, R. J. and Roila, F. (2010). Management of oral and gastrointestinal mucostis: ESMO Clinical Practice Guidelines. *Annals of Oncology*, 21, 262-265

- Shamseddine, A., Saleh, A., Charafeddine, M., Seoud, M., Mukherji, D., Temraz, S., & Sibai, A. M. (2014). Cancer trends in Lebanon: a review of incidence rates for the period of 2003–2008 and projections until 2018. *Population health metrics*, 12(1), 4.
- Sieracki, R., Voelz, L., Johannik, T., Kopaczewski, D., and Hubert, K. (2009). Development and implementation of an Oral Care Protocol for Patients with Cancer, *Clinical Journal of Oncology Nursing*, 13, 718-722.
- Silverman, S. (2007). Diagnosis and Management of Oral Mucositis. *The Journal of Supportive Oncology*, 5, 13-2.
- Stokman, M. A., Spijkervet, F. K., Boezen, H. M., Schouten, J. P., Roodenburg, J. L., de Vries, E. G. (2006). Preventive intervention possibilities in radiotherapy- and chemotherapy-induced oral mucositis: results of meta-analyses. *Journal of Dental Research*, 85(8), 690-700.
- Sonis, S. T., Eilers, J. P., Epstein, J. B., LeVeque, F. G., Liggett, W. H., Mulagha, M. T., Peterson, D. E., Rose, A. H., Schbert, M. M., Spijkervet, F. K., Wittes, J. P., for the mucositis study group (1999). Validation of a new scoring system for the assessment of clinical trial research of oral mucositis induced by radiation or chemotherapy. Mucositis Study Group. *Cancer*, 85(10), 2103–2113.
- Velez, I. (2004). Management of Oral mucositis induced by chemotherapy and radiotherapy: An update. *Quintessence international*, 35(2), 129-136.
- WHO Mucositis Grading Scales. Retrieved 2014, April 5th, from <http://www.gelclair.net/Institutional.aspx?Pagina=239&SM=230&Lingua=EN>
- Yarom, N., Ariyawardana, A., Hovan, A., Barasch, A., Jarvis, V., Jensen, S., Zadik, Y., Elad, S., Bowen, J., Lalla, R. (2013). Systemic review of natural agents for the management of oral mucositis in cancer patients. *Support Care Cancer*, 21(11), 3209-21.

# Appendix A

## Algorithm for Treatment of Oral Mucositis

