Prevention and Treatment of Mucositis: A Guide for Nurses

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Oral mucositis is a frequent and potentially severe complication that can occur following chemotherapy or irradiation. Not only is mucositis painful but it can also result in impaired nutrition, infection, and treatment delays. Pediatric oncology nurses have a challenge to try to provide the most appropriate mouth care regimen specific to each individual patient. This review of the literature can serve as a guide for helping to prevent and to treat mucositis. It provides information about the chemotherapeutic agents responsible for causing mucositis, many of the preventive approaches used to reduce the incidence of mucositis, and the current treatments available for active mucositis. It also discusses dietary recommendations and the role of the nurse caring for the patient with mucositis.

Key words: *mucositis, oral hygiene, mouthwash*

Sofia is a 4-year-old girl who is day +3 s/p a peripheral blood stem cell rescue for stage IV neuroblastoma. She received high-dose chemotherapy as part of the conditioning regimen and, as a result, has developed oral ulcers that have progressed to mucosal sloughing of her oral cavity. She is experiencing increasing pain, and she currently does not have a plan for oral hygiene. Sofia's WBC count is 0.1 (mm3), which means that she will have mucositis for a prolonged period of time, predisposing her to infection.

Oral mucositis is a frequent and potentially severe complication that can occur with chemotherapy. The discomfort associated with mucositis may impair communication, sleep, and oral intake. Furthermore, the patient's nutritional status may be further compromised, resulting in anorexia, cachexia, dehydration, and malnutrition. Complications related to mucositis may lead to costly hospitalizations, narcotics to control pain, and parental nutrition. In addition, mucositis decreases the patient's quality of life due to increased pain, and it causes treatment interruptions or dose reductions, provides the opportunity for infection to develop, and may affect a patient's compliance with other prescribed medications (Wilkes, 1998).

Currently, no intervention exists that is completely successful at preventing mucositis, and the standard of treatment for many years has been symptomatic care with analgesics, narcotics, and nutritional support. Recently there have been many new studies to help identify innovative strategies to help prevent and treat mucositis. The intent of this review of the literature is to provide a description of mucositis, discuss the most common chemotherapy agents responsible for mucositis, outline the current strategies to help prevent and treat mucositis, and stress the importance of an oral hygiene plan.

Chemotherapy-Induced Mucositis

Mucositis is caused by acute changes in the epithelium of the oral cavity resulting in the death of rapidly dividing epithelial cells. Chemotherapeutic agents inhibit the growth and maturation of oral mucosal cells and disrupt the primary mucosal barrier in the mouth and throat (Larson et al., 1998). The direct effects on

DOI: 10.1177/1043454204265840

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Table 1. Chemotherapeutic Agents Causing Mucositis

Alkylating Agents	*Antimetabolites*	*Nitrosureas*
Busulfan	Cytarabine	Carmustine
Cyclophosphamide	5-Fluorouracil	Lomustine
Ifosfamide	Hydroxyurea	
Melphalan	Mercaptopurine	
Procarbazine	Methotrexate	
Temozolamide	Thioguanine	
Thiotepa		
Anthracyclines	***Antineoplastic Antibiotics***	***Plant Alkaloids***
Daunomycin	Bleomycin Sulfate	Etoposide
Doxorubicin	Dactinomysin	Paclitaxel
Idarubicin		Vinblastine
Mitozantrone		Vincristine

the oral mucosa from chemotherapy can begin as early as 2 to 3 days after the administration of chemotherapy and generally peak in severity 7 to 10 days later, with resolution occurring within 2 weeks (Wilkes, 1998). Chemotherapeutic agents that produce mucositis are listed in Table 1.

Prevention of Mucositis

Mouthwashes

At the most basic level, the value of a mouthwash lies in its ability to wash away loose debris and moisten the oral mucosa. Mouthwashes should be nonirritating and nondehydrating to promote the optimal safe removal of debris (Miller & Kearney, 2001). A variety of studies have been done to help determine the most effective and safe mouthwash.

Many adult studies have demonstrated that chlorhexidine has the best antibacterial effects, which may be explained by the ability of chlorhexidine to exert this effect for as long as 12 hours (Miller & Kearney, 2001). However, Dodd et al. (1996) found that the use of chlorhexidine was no more effective than sterile water and that chlorhexidine, even though it is an antiplaque agent, can actually cause staining of the teeth and oral soft tissue if used for an extended period of time. Although the studies are conflicting, chlorhexidine is one of the most widely used mouthwashes.

Hydrogen peroxide continues to be used in clinical practice despite ongoing controversy. Tombes and Gallucci (1993) tested 35 healthy adults and found that hydrogen peroxide rinses were associated with mucosal abnormalities ($p < .001$) and elicited overwhelmingly negative subjective reactions. The individuals who tested both half and quarter strength hydrogen peroxide found that it exacerbated a dry mouth and was highly astringent causing stinging, pain, and nausea.

Normal saline is not an irritant and, therefore, may be more effective than a regimen using an astringent mouthwash. It does not irritate the oral mucosa nor does it change the salivary pH. Even though it is the least damaging mouthwash available, it has only been examined in a few research projects. A randomized, controlled trial was designed using adult patients who were to have 50% or more of the mouth irradiated as part of their treatment regimen for head and neck cancer. Forty patients were assessed weekly during their course of radiotherapy using an oral assessment guide. Twenty patients used normal saline rinses, and 20 used hydrogen peroxide. The patients who received the normal saline rinses began advanced oral care later than those receiving hydrogen peroxide ($p = .015$) (Feber, 1995). Normal saline is also safe, economical, and readily available (Miller & Kearney, 2001).

Sodium bicarbonate creates an alkaline environment that may have detrimental effects on the oral mucosa by allowing bacteria to multiply. Some researchers have hypothesized that sodium bicarbonate's unpleasant taste may have an impact on compliance, but further research is necessary (Miller & Kearney, 2001). A comparison of mouthwashes is found in Table 2.

Table 2. Mouthwashes—Pros and Cons

Mouthwashes	Pros	Cons
Chlorhexidine	Antimicrobial agent Suppresses oral microflora Decreased mucositis	Discoloration of teeth Epithelial desquamation Unpleasant taste Burning and stinging
G-MCSF rinses	Increases wound healing Reduces duration of mucositis	Needs further research
Hydrogen peroxide	Antibacterial agent Effective cleaning Debriding agent	Poor taste Irritation and burning Dries mucous membranes Damages granulation tissue Disrupts normal flora
Magnesium aluminum hydroxide, Diphenhydramine, Viscous lidocaine	Mucosal coating agent Analgesic effects Decreases oral acidity	Needs further research Dries mucous membranes
Normal saline	Cost effective Nonirritating Least damaging Promotes healing	Needs further research
Sodium bicarbonate	Debriding properties	Bacterial multiplication Unpleasant taste Burning

Mucosal Delivery Alterations

One of the ways of preventing mucositis is by altering the mucosal delivery and excretion of individual chemotherapeutic agents. Researchers have studied several different methods of slowing down saliva production, thus decreasing the amount of drug contact with the oral membranes.

Cryotherapy is the cooling of the oral mucosa with ice during the administration of chemotherapy. This is thought to produce temporary vasoconstriction, thus reducing the delivery of chemotherapy to the oral mucosa. A pilot study done in 1995 evaluated the efficacy of eating ice pops during high-dose melphalan (6-8 pops over 30 min) in hopes of reducing oral mucositis. There were 18 patients with a median age of 36.5 years (range 6-57). The patients started eating ice pops 5 minutes before initiating melphalan and continued until 5 minutes after the completion of the infusion. Only 1 out of 18 patients developed mucositis above grade 3/4 according to the World Health Organization (WHO) criteria. Even though there are not many studies done evaluating the use of ice pops, this therapy is inexpensive and accepted by both children and adults (Meloni, Capria, Proia, Trisolini, & Mandelli, 1996). Perhaps, in the near future more studies will be done evaluating the degree of mucositis related to the consumption of ice pops, allowing confirmation of these results.

Systemic allopurinol can attenuate 5-fluorouracil (5-FU) induced toxicity by inhibiting the enzyme orotidylate decarboxylase, thereby decreasing the formation of the metabolites fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP) (Loprinzi et al., 1990). After this report, a group of researchers developed an allopurinol mouthwash in hopes of having a protective effect against 5-FU. They performed a randomized, placebo-controlled, double-blinded crossover study. Seventy-seven adult subjects were assigned a mouthwash containing 20 mg of allopurinol or a placebo. The mouthwash was administered every hour for 4 hours beginning with each dose of chemotherapy. The severity of mucositis was graded on a scale of 0-4 by the attending physician and also by a patient-completed questionnaire.

There was a trend toward less mucositis in the placebo group, with physician-judged mucositis scores of 1.3 for placebo and 1.8 for allopurinol ($p = .07$) and mean patient-judged mucositis scores of 1.5 for placebo and 1.9 for allopurinol ($p = .15$). Results indicated that there were no substantial differences in mucositis when using an allopurinol mouthwash (Loprinzi et al., 1990).

Propantheline is a commercially available anticholinergic that decreases salivation and xerostomia (Wilkes, 1998). Etoposide is a commonly used chemotherapeutic agent that is excreted through the saliva. It was hypothesized that propantheline would decrease the incidence of mucositis. Twelve adult patients receiving etoposide as part of their pretransplant conditioning were randomized to receive propantheline or a placebo orally every 6 hours for a total of 6 doses. This study resulted in a reduction in the incidence and severity of mucositis in the patients who received the propantheline ($p = .05$) (Ahmed et al., 1993).

Modifiers of Mucosal Proliferation

It has been hypothesized that the rate of basal cell epithelial cell proliferation is correlated with the susceptibility of the mucosal tissues to the toxic effects of chemotherapy (Wilkes, 1998). Thus, researchers have studied various agents known to affect the epithelial proliferation.

Glutamine is a nonessential amino acid that is used primarily by the gastrointestinal tract as a major energy source for intestinal epithelium. It enhances nitrogen balance, decreases bacteremia, and helps diminish intestinal mucosal damage. A nonrandomized study was done in 2000 to determine the effect of glutamine suspension on mucositis associated with the administration of high-dose chemotherapy for bone marrow transplantation. The study included 21 adult women receiving high-dose paclitaxel and melphalan for metastatic breast cancer. The first 9 patients were the control group and did not receive any glutamine. The next 12 patients received a glutamine suspension as swish-and-swallow every 4 hours around the clock starting on day –7 and continuing until discharge from the hospital or until the mucositis resolved, averaging about 16.17 days. Mucositis was graded by the attending physician according to the National Cancer Institute Common Toxicity Criteria. The primary outcomes measured were the total days of mucositis, the highest grade of mucositis observed, the number of days TPN was administered, and the number of days parenteral or transdermal narcotics were required. Results revealed that the group of patients who received glutamine suspension every 4 hours around the clock had significantly fewer days of mucositis ($p = .037$) and a lower maximum grade of mucositis ($p = .046$). They also did not require a patient-controlled analgesia (PCA) for pain ($p = .002$) (Cockerham, Weinberger, & Lerchie, 2000).

Beta-carotene, a vitamin A derivative, has inhibitory effects on cellular proliferation. A study done with 20 adult patients (mean age = 57 years) receiving chemotherapy and radiation for oral cancer were randomized to receive supplemental beta-carotene. Patients were given vincristine, bleomycin, and methotrexate, followed by radiation 60 Gy in 30 fractions over an 8-week period. Beta-carotene dosage began at 250 mg daily up to day 21 and then 75 mg daily for the duration of treatment. The severity of mucositis was scored weekly by the consensus among three observers according to the grading system used by Tygerberg Hospital Head and Neck Oncology Clinic (Grades 0 to 4). Although both groups had severe mucositis, the group receiving the supplemental beta-carotene developed these severe reactions 6 weeks later and these reactions tended to be less intense than the control group ($p < .025$) (Mills, 1988).

Prostaglandins protect the gastric and intestinal mucosa when given before ulcerogenic compounds such as a nonsteroid anti-inflammatory drug. Additionally, prostaglandin E1 and E2 have been reported to have cytoprotective effects on a variety of tissues and have been tested as a mucosal protectant for patients receiving high-dose chemotherapy. A group of 15 patients, ranging in age from 16 to 68 years with a median age of 35, undergoing a stem cell transplant with high-dose chemotherapy, were randomized to receive either oral misoprostol (E1 synthetic analogue) or a placebo. Patients were given misoprostol 250 mcg three times a day by mouth starting on day –4 and continuing until day +16. The same investigator graded mucositis daily according to the WHO Toxicity Criteria. The mucositis incidence was significantly higher in the group that received the misoprostol, with a p value of .0001 (Duenas-Gonzalez et al., 1996). Another study was done between October 1988 and December 1990 to evaluate the use of prostaglandin E_2 (PGE) for prophylaxis of oral mucositis following bone marrow transplant. The study was a double-blinded prospective

randomized study involving 60 patients with leukemia undergoing bone marrow transplant, ranging in age from 5 to 43 with a median age of 31. Patients were given either placebo or PGE tablets three times a day starting day –7 and continuing to day +21. The degree of mucositis was recorded by one of two investigators according to the WHO criteria for oral toxicity. Patients were also screened weekly for herpes simplex virus (HSV) through throat cultures. Results indicated that the use of a PGE tablet did not increase or decrease the severity or duration of mucositis. The highest incidence of severe oral mucositis was found in patients with HSV infection receiving PGE tablets $p = .009$ (Labar et al., 1993).

Antimicrobial

It has been theorized that the reduction of bacteria-causing agents in the oropharynx may result in a decreased incidence of mucositis and stomatitis. Oral antimicrobial agents have been studied for the prevention of radiation- and chemotherapy-induced mucostitis.

Lozenges containing polymyxin E, tobramycin, and amphotericin B have been used to eradicate selectively aerobic gram-negative bacteria and yeasts from the aerobic flora. One study hypothesized that the severe forms of radiation-induced mucositis were related to the amount of bacteria present in the oropharynx. The group of 136 adult patients who received the lozenges experienced a reduction in mucositis distribution ($p = .002$), and area ($p = .028$), less dysphagia ($p = .006$), and less weight loss ($p = .009$) (Symonds et al., 1996). Another study included 112 adult patients who were randomized to receive either an antibiotic lozenge or a placebo. Results indicated that there were no substantial differences or trends in the mucositis scores ($p = .02$); however, the duration of patient-reported mucositis was slightly less in the group that received the lozenges (median 2.7 weeks vs. 3.7 weeks; $p = .04$) (Okuno et al., 1997).

The chamomile plant has been used for medicinal purposes for centuries. Data suggest that the compounds derived from this plant have anti-inflammatory, antibacterial, and antifungal properties (Wilkes, 1998). A group of 164 adult patients receiving 5-FU were randomized to receive a chamomile or placebo mouthwash three times a day for 14 days. Results indicated that there was no difference of 5-FU-induced mucositis between the two groups, $p = .43$ (Fidler et al., 1996).

Treatment of Mucositis

The management of established mucositis can be difficult for both the patient and the provider. Mucositis can be extremely painful, and finding the appropriate intervention for each specific patient can be a challenge. There are several agents that have recently been investigated to help with the treatment of mucositis.

Sucralfate is a basic albumin salt of sucrose octasulfate that has been approved for use in the treatment of patients with an active duodenal ulcer. It adheres to the exposed protein in inflamed gastroduodenal mucosa thus providing a protective coat against pepsin and possibly acid. A study including 50 adult patients with active mucositis caused by 5-FU were randomized to receive either a sucralfate solution or a placebo in hopes of alleviating mucositis and stomatitis. The results indicated that there was no difference in severity or duration of mucositis or stomatitis on either protocol arm ($p = .99$ and .88, respectively) (Loprinzi et al., 1997).

Oral suspensions of magnesium hydroxide have frequently been used for established mucositis because it adheres to surfaces and reduces oral acidity, dissolves mucin film, and in some cases provides symptomatic relief. However, routine use of this agent is not recommended because it tends to produce excessive drying of the mucous membranes (Weisdorf et al., 1989).

Vitamin E has been found to be effective in the treatment of gingivostomatitis. A randomized, double-blind placebo-controlled study was done to determine whether topical Vitamin E would be effective in healing mucositis. A total of 18 adult patients receiving chemotherapy for various types of malignancies were included in this study. Six of the nine patients who received Vitamin E had complete resolution of their oral lesions compared with only one out of nine patients who received the placebo ($p = .025$). These results suggest that Vitamin E may be effective therapy, but more studies with a larger number of patients need to be done to verify this initial preliminary finding (Wadleigh et al., 1992).

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is commonly administered to patients after chemotherapy to reduce the duration of drug-induced

Table 3. Dietary Guidelines for Patients With Mucositis

General Guidelines	
Small pieces of food	
Use straw with liquids	
Nutritional supplements (eg, Boost, Scandishake, Ensure)	
Topical analgesics prior to eating	
Mouthwash following meals	
Avoid hot foods	
Recommended	***Not Recommended***
Tepid or cool liquids	Spicy, salty, bitter foods
Puddings, Jell-O	Dry foods (crackers, toast, chips)
Cottage cheese, soft cheeses	Oranges, grapefruits, citrus fruits
Bananas, peaches, applesauce	Chewing gum, candy
Milkshakes, smoothies	
Popsicles, ice cubes, Italian water ice	

neutropenia and to enhance leukocyte activity. Animal studies have demonstrated that topical application of GM-CSF on acute and chronic wounds increases the rate of wound closure (Robson et al., 1994). In view of this information, it was hypothesized that GM-CSF mouthwash could potentially reduce the duration of severe oral mucositis in patients receiving high-dose chemotherapy. The study group consisted of 10 adult patients suffering from severe oral mucositis as a result of chemotherapy used during bone marrow transplantation. They used GM-CSF mouthwash three times a day after standard mouth care until the dentist determined clinical resolution of oral lesions. Standard mouth care consisted of oral debridement with gauze dipped in sterile saline solution with sodium bicarbonate, topical miconazole oral gel, and 0.12% chlorhexidine gluconate mouthwash. The control group of 29 patients performed the standard mouth care. The duration of mucositis appeared to be reduced; 60% of the GM-CSF mouth rinse patients had severe mucositis but for less than 9 days, whereas 28% of the control patients had severe mucositis for less than 9 days and the remainder of the control patients had severe mucositis for > 9 days. These findings suggest that GM-CSF may reduce the duration of severe mucositis, but more clinical trials are now required (Bez et al., 1999).

Some providers recommend topical analgesics in combination with mucosal coating agents. The main treatment of choice is a mouthwash containing a mixture of magnesium aluminum hydroxide, diphenhydramine, and viscous lidocaine. There are currently no solid clinical data to support or reject the routine use of this commonly used mouthwash.

Diet

Maintaining adequate caloric intake in the face of severe mucositis can be a challenge. It is best to limit the amount of contact between food and the irritated mucosa; therefore, a diet containing items such as Jell-O, pudding, milkshakes, and so on, that require little chewing is recommended. Also, avoiding highly acidic, salty, bitter, and spicy foods is recommended. Table 3 provides some dietary guidelines for patients with mucositis.

Nursing Implications

Oral care is an integral part of basic nursing practice. However, it has become a topic of conflicting advice and subjective conclusions taken from sporadic research. Rarely is oral care taught to families and patients, but it is something that is frequently delegated to junior staff such as nursing assistants and nursing students (Miller & Kearney, 2001). Due to the frequency of unavoidable mucositis, oral care is a particular priority for nurses caring for children with cancer.

The first step of mouth care involves a thorough oral assessment prior to initiation of therapy and then at least daily following the chemotherapy. This will ensure early identification of any oral lesions. The second step involves creating an oral care plan that involves cleaning the teeth and the use of a mouthwash tailored specifically to each patient. Many studies have shown that increasing the frequency of oral care will help reduce the patient's potential for infection, ensure

patient comfort, and reduce mouth care problems (Miller & Kearney, 2001). Last, the addition of some of the previously discussed treatments for mucositis can be initiated. The challenge lies in finding the most appropriate oral care regimen for each patient and using it consistently.

It is the nurse's role to provide or supervise oral care. Through the appropriate application of research and knowledge, the practice of oral hygiene can provide comfort and prevent complications that can affect a patient's quality of life. Patient education and participation is crucial because of the fact that most chemotherapy is delivered in the outpatient setting. It is hoped that through this review of the literature, nurses will be in a better position to help determine the most appropriate oral care for their patients.

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