A Research Review of the Current Treatments for Radiation-Induced Oral Mucositis in Patients With Head and Neck Cancer

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Purpose/Objectives: To review the research studies on the current treatments for radiation therapy- (RT-) induced mucositis in patients with head and neck cancer.

Data Sources: MEDLINE® search of the literature from 1966–2001.

Data Synthesis: Four types of agents (i.e., antimicrobial, coating, anti-inflammatory, and cytokine-like agents) have been evaluated for the management of RT-induced oral mucositis in patients with head and neck cancer. Most of the published studies had relatively small sample sizes and used inconsistent measures to evaluate the extent and severity of oral mucositis. Therefore, definitive conclusions regarding the effectiveness of any of the agents tested in the prevention and treatment of RT-induced oral mucositis cannot be drawn.

Conclusions: Oral mucositis remains the most common complication among patients with head and neck cancer. Although a number of strategies and products are being investigated and new directions are promising, the therapies tested to date have not produced consistent results.

Implications for Nursing: The most effective measure to treat RT-induced mucositis in patients with head and neck cancer is frequent oral rinsing with a bland mouthwash, such as saline or a sodium bicarbonate rinse, to reduce the amount of oral microbial flora. Dental care, consistent oral assessments, and the initiation of a standardized oral hygiene protocol before the initiation of cancer treatment are the most effective approaches for oral mucositis.

Goal for CE Enrollees:

To further enhance nurses' knowledge in the current treatment for radiation therapy-induced oral mucositis.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Describe treatment regimens currently available for the treatment of radiation therapy-induced oral mucositis.
2. Describe research limitations discovered during review of current treatments for radiation therapy-induced mucositis.
3. Discuss the nurse's role in the care of patients with radiation therapy-induced oral mucositis.

Key Points . . .

- More than 50 published papers document the clinical investigations aimed at the prevention, palliation, or reduction of radiation therapy- (RT-) induced oral mucositis in patients with head and neck cancer.
- Antimicrobial, coating, anti-inflammatory, and cytokine-like agents are the main modalities used in the treatment of RT-induced oral mucositis.
- Based on the findings of the studies conducted to date, concluding whether antimicrobials, coating agents, or anti-inflammatory agents decrease the severity of RT-induced oral mucositis is not possible.
- Promising new treatments that include the use of cytokine mouthwashes may facilitate epithelial healing and maturation during RT.

According to the National Institutes of Health (NIH) Consensus Development Panel (1990), the prevention and treatment of oral complications associated with radiation therapy (RT) and chemotherapy should include dental treatment before cancer treatment and the use of antimicrobial and cytoprotective mouth rinse agents during therapy. The use of cleansing agents (e.g., saline, sterile water, sodium

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bicarbonate solution) is well recognized as preventive care for patients at risk for cancer treatment-induced mucositis. Cleansing agents ensure the safe removal of loose debris and keep the damaged oral mucosa clean. Sodium bicarbonate reduces the acidity of the oral fluids immediately; it also dilutes accumulating mucus and discourages yeast colonization (Carl & Emrich, 1991).

A wide variation in treatment approaches for oral mucositis exists. For example, Mueller, Millheim, Farrington, Brusko, and Wiser (1995) conducted a survey to identify the national treatment practices for chemotherapy- or RT-induced oral mucositis among patients with cancer and to compare these practices to NIH guidelines. The researchers mailed surveys to clinical pharmacists in 200 hospitals throughout the United States. Thirty-one percent (n = 62) of the 200 questionnaires were completed and returned from 42 states. Most of the respondent institutions were university-based medical centers (48%), and 45% of the hospitals ranged in size from 500–750 beds. Institutions used a wide range of agents, which generated substantial variability in mucositis prophylaxis and treatment protocols. Sixty-nine percent indicated that their hospitals did not use a standardized protocol for the treatment of oral mucositis. Eighty-two percent of the protocols included a single agent or combinations of ingredients (e.g., mouthwash mixture of hydrogen peroxide, saline, water, salt, and soda; nystatin) that lack proven clinical efficacy. Mueller et al. concluded that oral mucositis management strategies for hospitalized patients varied widely among U.S. hospitals. Coordinated, controlled studies are needed to identify optimal therapies for patients who receive stomatotoxic chemotherapy or RT to the oral mucosa.

More than 50 published papers document the clinical investigations aimed at the prevention, palliation, or reduction of RT-induced oral mucositis in patients with head and neck cancer. Most of the treatments are merely palliative or are directed at secondary problems, such as infections or pain (Madeya, 1996; NIH Consensus Development Panel, 1990; Raber-Durlacher, 1999).

Four major types of agents constitute the main modalities used in the management of RT-induced mucositis: antimicrobial agents, coating agents, anti-inflammatory agents, and cytokine-like agents (Madeya, 1996; Miaskowski, 1990; Sonis, 1998; Verdi, 1993). This article will review the research studies about the current treatments for RT-induced oral mucositis in patients with head and neck cancer. A MEDLINE® search was conducted for the years 1966–2001 to obtain a list of all of the research studies written in English that evaluated treatments for RT-induced oral mucositis in patients with head and neck cancer. Additional papers were found based on a careful review of the reference lists from the studies identified through the MEDLINE search. The search revealed that the range of agents used for a mucositis indication is extensive. This article addresses the efficacy of these four types of agents in the prevention and treatment of RT-induced oral mucositis. Implications for practice are drawn from this review.

Antimicrobial Agents

The major antimicrobial or antiseptic agents include benzydamine (BZD), chlorhexidine, hydrogen peroxide, and antibiotic lozenges of polymixin B, tobramycin, and amphotericin B (PTA lozenge). They work by inhibiting the growth of abnormal microflora and can result in a decrease in the number of opportunistic infections, which may reduce the severity of RT-induced mucositis.

Benzydamine

BZD is a nonsteroidal drug with analgesic, anesthetic, anti-inflammatory, and antimicrobial properties (Epstein, 1990; Verdi, 1993). BZD inhibits the chemical mediators of inflammation, including prostaglandins, serotonin, histamine, and acetylcholine. The mechanism of action of BZD is believed to be the stabilization of cellular and intracellular membranes through inhibition of platelet aggregation and degranulation of polymorphonuclear leukocytes (Epstein).

Six double-blind, placebo-controlled, randomized clinical trials have been published that evaluated the use of BZD in the management of the RT-induced mucositis in patients with head and neck cancer. These studies are summarized in Table 1. Two studies evaluated the efficacy of BZD in patients with head and neck cancer receiving intra-arterial chemotherapy (Prada & Chiesa, 1987; Prada, Lozza, Moglia, Sala, & Chiesa, 1985). Three studies examined its efficacy during RT (Epstein & Stevenson-Moore, 1986; Epstein, Stevenson-Moore, Jackson, Mohamed, & Spinelli, 1989; Kim, Chu, Lakshmi, & Houde, 1985), and one study compared the effects of BZD to chlorhexidine (Samaranayake et al., 1988).

The main outcome measures in these six studies were the time to onset of mucositis and severity of mucositis and oral pain; however, the findings across these six studies are inconsistent. Only three studies described a decrease in the severity of mucositis with BZD compared to placebo (Epstein et al., 1989; Kim et al., 1985; Prada et al., 1985), and only one study described a delay in the onset of mucositis (Prada & Chiesa, 1987). The findings on pain severity also were inconsistent as only two of the placebo-controlled trials noted a decrease in pain with BZD use (Epstein & Stevenson-Moore, 1986; Kim et al.). However, in the comparative trial of chlorhexidine and BZD by Samaranayake et al. (1988), the patients reported more discomfort (i.e., burning and nausea) with BZD and were more likely to discontinue participation in the trial.

Two of the six papers were pilot studies (Epstein & Stevenson-Moore, 1986; Prada et al., 1985), and the results of larger studies were published subsequently (Epstein et al., 1989; Prada & Chiesa, 1987). The majority of the studies had relatively small sample sizes that ranged from 20–67 patients, and none of the studies published power calculations. In all probability, because of their small sample sizes, several of the studies did not have sufficient power to detect significant differences with the use of a BZD rinse compared to placebo. The scale used to measure the severity of mucositis had a single item in all but two of the studies (Epstein et al.; Epstein & Stevenson-Moore). A single-item scale may lack sufficient sensitivity to detect changes in the severity of mucositis over time.

Differences in the frequency and duration of the outcome measurements in relationship to the course of RT make determining the effectiveness of BZD difficult. Some studies have measured various outcomes daily for only 4–10 days, whereas others have evaluated outcomes weekly for the duration of RT. Variation in the length of time that patients used a BZD rinse also make interpreting its effectiveness difficult. Based on the small number of studies, small sample sizes, and numerous confounding factors, concluding whether BZD is

Table 1. Management of Radiation-Induced Mucositis With Benzydamine

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Kim et al. (1985)	Determine the analgesic and anti-inflammatory effectiveness of benzydamine (BZD) as a rinse or gargle in patients with radiation therapy-induced mouth and/or throat pain.	Double-blind, placebo-controlled, randomized clinical trial (BZD = 37, placebo = 30)	**Objective:** Measured daily for four days Severity of mucositis and hyperemia **Subjective:** Measured daily for four days **Symptoms:** Patient diary of pain with and without swallowing (0 = none to 4 = severe), difficulty eating (0 = none to 4 = severe), and relief of pain with and without swallowing (0 = none to 5 = complete)	**Mucositis severity:** Significant reduction in severity of mucositis between days two and three was found in the BZD group. **Symptoms of mucositis:** Significant reduction in pain with swallowing and inability to eat were reported in the BZD group.
Prada et al. (1985)	Ascertain whether BZD had histoprotective and anti-inflammatory effects on the oral mucosa during intra-arterial chemotherapy for head and neck cancer.	Double-blind, placebo-controlled, randomized clinical trial (BZD = 10, placebo = 10)	**Objective:** Measured daily for 10 days **Mucositis signs:** Hyperaemia, edema, epitheliolysis, and necrosis (0 = absent to 3 = severe) **Subjective:** Measured daily for 10 days **Mucositis symptoms:** Patient's ratings of burning, spontaneous pain, pain while eating, dysphagia (0 = absent to 3 = severe)	**Mucositis severity:** Nonsignificant differences in the severity of mucositis were reported between groups. **Symptoms of mucositis:** BZD group reported nonsignificant changes with a maximum decrease of 14.7% at the end of treatment. Control group reported a significant increase in symptoms at the end of radiation therapy ($p < 0.05$).
Epstein & Stevenson-Moore (1986)	Determine the effectiveness of BZD in patients receiving radiation therapy to the oropharyngeal region of cancer.	Double-blind, placebo-controlled, randomized clinical trial (BZD = 18, placebo = 11)	**Objective:** Measured weekly **Mucositis severity:** No description of scale **Subjective:** Measured weekly **Pain:** Intensity was measured using a Visual Analog Scale.	**Mucositis severity:** No differences were found between groups. **Pain:** A significantly lower intensity of pain was reported in the BZD group ($p < 0.05$). **Pain medicine:** Significantly fewer patients in BZD group required systemic analgesics and viscous lidocaine use ($p < 0.05$).
Prada & Chiesa (1987)	Investigate whether the anti-inflammatory activity of BZD also could protect the oral mucosa from the dystrophic damage caused by selective intra-arterial chemotherapy.	Double-blind, placebo-controlled, randomized clinical trial (BZD = 19, placebo = 17)	**Objective:** Measured daily for 10 days **Signs of mucositis:** Hyperaemia, edema epitheliolysis, and necrosis (0 = absent to 3 = intense or remarkable) **Subjective:** Measured daily for 10 days 1. **Symptoms of mucositis:** Burning, spontaneous pain, pain caused by chewing, dysphagia, odynophagia (0 = absent to 3 = intense or remarkable) 2. Global score of clinical symptomatology is the score of signs plus the score of symptoms.	**Onset of the mucositis:** Significant delay occurred with the use of BZD (six days versus three days after chemotherapy, $p < 0.01$). **Global clinical symptomatology score:** The score was unchanged in the BZD group, but it increased significantly in the control group.
Samaranayake et al. (1988)	Compare the efficacy of BZD and chlorhexidine in alleviating radiation therapy-induced mucositis.	Randomized clinical trial (BZD = 12, chlorhexidine = 13)	**Objective:** Measured weekly 1. **Mucositis:** Graded using a 0–4 scale (i.e., none, mild, moderate, severe, ulceration). 2. **Oral flora:** Candida, coliforms, staphylococcus	**Mucositis severity or intensity of pain:** No significant differences were found. **Toxicities associated with rinse:** More were reported in chlorhexidine group compared

(Continued on next page)

Table 1. Management of Radiation-Induced Mucositis With Benzydamine *(Continued)*

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
			Subjective: Measured weekly 1. **Pain:** Intensity measured using a Visual Analog Scale (0–100 mm) 2. **Toxicities with rinse:** Symptoms of burning, nausea, discontinuation of use, interruption of radiation therapy, pain associated with rinse use	with the BZD group (e.g., burning, nausea, discontinuation of rinse, interruption of radiation therapy, pain associated with rinse use). **Carriage rates of microflora:** No significant differences were found.
Epstein et al. (1989)	Study the use of BZD in patients receiving radiation therapy to the oropharyngeal region of cancer.	Double-blind, placebo-controlled, randomized clinical trial (BZD = 25, placebo = 18)	**Objective:** Measured weekly **Mucositis:** Each area of mucosa was scored using a 0–3 scale (0 = none to 3 = severe) that considered the severity of inflammation, severity of ulceration, and maximum size of ulceration. **Subjective:** Measured weekly **Symptoms:** Visual Analog Scale ratings for burning, pain at rest, pain with eating, anesthetic effect	**Mucositis:** BZD group had a lower total mucositis score ($p = 0.001$), smaller average area and smaller maximum mucositis score ($p = 0.05$), smaller maximum size of ulceration ($p = 0.04$), and smaller total area of ulceration ($p = 0.05$). **Pain:** Trends reported were less pain in the BZD group at rest ($p = 0.08$) and less pain with eating ($p = 0.09$). More patients experienced pain reduction ($p = 0.07$), and more reported anesthesia ($p = 0.10$).

effective in reducing the severity of RT-induced mucositis or the severity of pain associated with RT to the oral mucosa is not possible.

Chlorhexidine

Chlorhexidine is a bisbiguanide that is used to control plaque-dependent oral disease, such as caries and gingivitis (Ferretti, Brown, Raybould, & Lillich, 1990). Chlorhexidine is effective against gram-positive and gram-negative bacteria, as well as against yeast and fungal organisms (Ferretti, Brown, et al.; Verdi, 1993). Three double-blind, placebo-controlled clinical trials have evaluated the efficacy of chlorhexidine as a preventive agent for RT-induced mucositis in patients with head and neck cancer (Ferretti, Raybould, et al., 1990; Foote et al., 1994; Spijkervet et al., 1989). The results of these studies are summarized in Table 2.

The main outcome measures in the three trials were the severity of mucositis, an assessment of the microbial flora in the oral cavity, and the toxicities associated with the chlorhexidine mouthwash. Chlorhexidine was not effective in reducing the severity of mucositis in any of the studies. However, Foote et al. (1994) reported a trend toward more severe mucositis and a significantly higher proportion of patients with toxicities (e.g., discomfort, taste alterations) with the chlorhexidine rinse compared to a vehicle placebo. In addition, two trials that examined antimicrobial activity failed to show any significant effects on the suppression of any type of oral flora using the chlorhexidine mouth rinse (Ferretti, Raybould, et al., 1990; Spijkervet et al., 1989).

Some limitations with the chlorhexidine studies are worth noting. First, the sample sizes in the three studies were moderately small, and none of the studies included a power analysis. In addition, the mucositis measures in two studies (Ferretti, Raybould, et al., 1990; Foote et al., 1994) were based on a single-item scale, and this measure did not account for the extent of the mucositis when calculating a severity score. Similarly, this measure may lack sufficient sensitivity to detect changes in the severity of mucositis over time.

Topical Antibiotic Agents—Lozenge and Adhesive Film

Although some investigators have evaluated the use of chlorhexidine and BZD for their broad antimicrobial effects in an attempt to prevent mucositis through elimination of microbial flora in the oral cavity, four studies investigated the effectiveness of using topical antibiotics with a more specific spectrum for gram-negative bacteria and yeast (Oguchi et al., 1998; Okuno et al., 1997; Spijkervet et al., 1990; Symonds et al., 1996). Two placebo-controlled, randomized clinical trials, one by Okuno et al. (N = 112) and the other by Symonds et al. (N = 221), and one case-controlled clinical trial by Spijkervet et al. (1990) (N = 15) investigated the efficacy of the PTA lozenge in reducing the severity of RT-induced mucositis.

The clinical trial conducted by Oguchi et al. (1998) evaluated the efficacy of a mucosa-adhesive water-soluble polymer (AD) film that contained an anesthetic (tetracaine) and antibiotics (ofloxacine, miconazole, guaiazulene, and triacetin) to alleviate pain and prevent secondary oral infections related to RT-induced oral mucositis. The AD film was placed on the oral area when needed to control pain induced by oral mucositis.

The findings from the studies without placebo-controls by Oguchi et al. (1998) and Spijkervet et al. (1990) were compared with previous groups of patients who did not receive the study agents. In all four studies, patients followed a standardized oral hygiene protocol in addition to using the test agent (Oguchi et al.; Okuno et al., 1997; Spijkervet et al., 1990; Symonds et al., 1996). These four studies are summarized in Table 3.

Table 2. Management of Radiation-Induced Mucositis With Chlorhexidine

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Spijkervet et al. (1989)	Study the antimicrobial effects of chlorhexidine (CHD) (0.1%) use on oropharyngeal flora associated with radiation therapy mucositis.	Double-blind, placebo-controlled, randomized clinical trial (CHD = 15, placebo = 15)	**Objective:** 1. **Mucositis severity:** Measured three times weekly; calculated for eight areas in oral cavity using four signs (white discoloration, erythema, pseudomembranes, and ulceration) and their extent 2. **Oral microflora:** Culture from oral gargling method, twice at baseline and three times weekly during radiation therapy: *varidance streptococci, staphylococci epidermidis, staphylococci aureus, staphylococci faecalis, candida species, and enterobacteriaceae/pseudomonadaceae/acinetobacter species*	**Severity of oral mucositis:** No significant differences were found. **Oral microflora:** No significant differences were found in suppression of any type of oral microflora.
Ferretti, Raybould, et al. (1990)	Evaluate the use of CHD (0.12%) for prophylaxis of oral stomatitis in patients with cancer receiving radiation therapy for head and neck cancer.	Double-blind, placebo-controlled, randomized clinical trial (CHD = 16, placebo = 14)	**Objective:** Measured at days 7, 14, and 21 after the initiation of therapy and at one week after discontinuation of the rinse 1. **Mucositis scoring index:** 0 = no ulceration, 1 = one or two small (< 1 cm) ulcerations, 2 = more than two small ulcerations, 3 = two or more larger (> 1 cm) ulcerations, 4 = multiple ulcerations 2. **Oral microbial flora:** Swab culture for streptococci, yeast, and gram-negative bacilli	**Mucositis:** No significant differences in mucositis incidence or severity were found between CHD and control groups. **Microflora:** CHD rinse showed a trend toward decreasing the counts of streptococci and yeast.
Foote et al. (1994)	Evaluate the effects of CHD in preventing and alleviating radiation therapy-induced oral mucositis.	Double-blind, placebo-controlled randomized clinical trial (CHD = 27, placebo = 25)	**Objective:** Measured weekly **Mucositis:** World Health Organization grading criteria (0 = none, 1 = soreness, erythema, 2 = erythema, ulcers, solid food, 3 = ulcers, liquid diet only, 4 = alimentation not possible) **Subjective:** Measured weekly **Toxicities associated with CHD use:** Taste alteration, teeth staining, discomfort	**Mucositis:** Slightly worse severity was reported in the CHD group. **Toxicities:** More patients in CHD group reported mouthwash-induced discomfort and taste alteration ($p < 0.0001$) and teeth staining ($p < 0.05$) compared to the placebo group.

The major outcome measures in the three studies of the PTA lozenge were severity of mucositis, oral pain or dysphagia associated with mucositis, and the presence or absence of oral infections. Spijkerver et al. (1991) and Symonds et al. (1996) documented a significant decrease in the severity of mucositis. However, only Symonds et al. demonstrated a reduction in the colonization of yeast in the oral mucosa by using the PTA lozenge. Additional work is warranted to determine the effects of the PTA lozenge on mucositis severity, pain severity, and dysphagia.

Okuno et al. (1997) were unable to find a difference in the severity of mucositis, which may be explained by the use of a single-item scale to grade the severity of mucositis. This scale may lack the sensitivity to detect differences in mucositis. An additional confounding variable in Okuno et al.'s study was the 20 mg dose of polymixin E (colistin) that was used compared to the 2 mg dose used in the trials by Spijkervet et al. (1991) and Symonds et al. (1996). Okuno et al. did not explain why differences in efficacy were observed in the previous two studies with the PTA lozenge.

In the study of the efficacy of AD film, significantly higher rates of complete pain relief at rest and while eating were present, and no secondary infections were reported in the AD film group. Also, the use of AD film was found to reduce the colonization of yeast in the oral mucosa. However, the severity of mucositis was not reduced nor was the intensity of pain. Because only one study was conducted using the AD film, attempting to draw definitive conclusions regarding the effectiveness of this modality for the treatment of RT-induced mucositis is not possible.

Table 3. Management of Radiation-Induced Mucositis With Topical Antimicrobial Agents

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Spijkervet et al. (1991)	Investigate the effect of selective elimination of gram-negative bacilli from the oral cavity on mucositis using antibiotic lozenges containing 2 mg of polymyxin E, 1.8 mg of tobramycin, and 10 mg of amphotericin B (PTA lozenge) administered four times per day starting with the first day of irradiation for five consecutive weeks during radiation therapy.	Pilot study. Patients (n = 15) were compared to another group of patients who received either a chlorhexidine rinse (n = 15) or a placebo rinse (n = 15) in a previous study (Spijkervet et al., 1990).	**Objective:** Measured three times weekly 1. **Mucositis:** Severity was calculated for eight areas in the oral cavity using four signs (white discoloration, erythema, pseudomembranes, and ulceration) and their extent. 2. **Oropharyngeal microflora:** Carriage rates and colonization index	**Mucositis:** A significant decrease in the severity of mucositis was found in the PTA group ($p < 0.05$) compared to either the chlorhexidine or placebo groups. **Microbial flora:** In all patients using PTA lozenges, eradication of gram-negative bacilli and yeast were achieved within three weeks.
Symonds et al. (1996)	Test the hypothesis that more severe forms of radiation therapy-induced mucositis are associated with aerobic gram-negative bacteria and yeasts and that selective reduction of microbial population with nonabsorbable antibiotic PTA lozenge containing 2 mg of polymyxin E, 1.8 mg of tobramycin, and 10 mg of amphotericin B would reduce the signs and symptoms of mucositis, dysphagia, and weight loss. The PTA lozenge was administered four times per day from the first day of radiation therapy until radiation therapy was completed.	Double-blind, placebo-controlled, randomized clinical trial (PTA lozenge = 112, placebo = 109)	**Objective:** Measured weekly 1. **Mucositis:** Percentage of area; the distribution is patchy or confluent; the type of membrane is none, thin, opalescent, intermediate, or thick; the degree of erythema is characterized as none, slight, moderate, or severe. 2. **Oral pharyngeal bacterial flora:** Sampled twice weekly 3. **Percentage of weight loss** **Subjective:** Measured weekly 1. **Pain on swallowing:** None, slight, moderate, or severe 2. **Dysphagia:** None, some discomfort or no dietary disturbance, difficulty swallowing and needs a soft diet, considerable difficulty and needs a liquid diet, severe difficulty and needs nasogastric or IV feeding	**Mucositis:** Use of a PTA lozenge resulted in a significant decrease in mucosal erythema ($p < 0.06$), distribution of mucositis ($p < 0.002$), and area of mucositis ($p < 0.03$). **Dysphagia, weight loss, and pain:** Use of a PTA lozenge resulted in a significant decrease in the severity of dysphagia ($p < 0.006$), percentage of weight loss ($p < 0.009$), and a trend for decreasing pain. **Microbial flora:** Using a PTA lozenge resulted in a significant reduction in the percentage of patients with yeast ($p < 0.01$); no significant reduction in the percentage of patients with aerobic gram-negative bacteria was reported between the two groups.
Okuno et al. (1997)	Determine whether a prophylactic antibiotic PTA lozenge containing 20 mg of polymyxin E, 1.8 mg of tobramycin, and 10 mg of amphotericin B could alleviate radiation therapy-induced mucositis. The PTA lozenge was administered four times per day	Double-blind, placebo-controlled, randomized clinical trial (PTA lozenge = 54, placebo = 58)	**Objective:** Measured weekly 1. **Mucositis:** World Health Organization criteria (0 = none, 1 = soreness or erythema, 2 = erythema or ulcers and needs solid food, 3 = ulcers and needs a liquid diet only, 4 = alimentation not possible) 2. **Treatment interruption:** Days **Subjective:** Measured weekly 1. **Patient self-report** of severity of mucositis 2. **Toxicities** associated with loz-	**Mucositis:** No significant difference in mucositis scores reported by clinician was found between the two groups. **Patient-report mucositis:** Significantly lower mean mucositis score in the PTA group ($p < 0.05$) and a shorter duration of acute grade 2–4 mucositis were found. **Treatment interruptions:** No significant differences in the number of days treatment was inter-

(Continued on next page)

Table 3. Management of Radiation-Induced Mucositis With Topical Antimicrobial Agents *(Continued)*

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
	during the course of radiation therapy and for two subsequent weeks.		enge (i.e., burning, discomfort, pain, taste alteration, teeth-staining)	rupted were reported between the two groups. **Symptoms:** No significant differences in toxicities were reported between the two groups.
Oguchi et al. (1998)	Evaluate the usefulness and safety of a mucosa-adhesive water-soluble polymer film (AD film) containing anesthetics and antibiotics (i.e., tetracaine, ofloxacine, miconazole, guaiazulene, and triacetin) for the treatment of radiation therapy-induced mucositis, alleviation of pain, and prevention of secondary infection.	Patients who used the AD film were compared to a previous group of patients who used only topical anesthetics (AD film = 25, control = 27).	**Objective:** Assessed during the second half of radiation therapy 1. **Mucositis:** Radiation Therapy Oncology Group acute radiation morbidity scoring criteria (0 = none, 1 = infection, 2 = patchy mucositis or inflammatory discharge, 3 = confluent, 4 = ulceration hemorrhage or necrosis) 2. **Presence of oral infections** **Subjective:** Assessed during the second half of radiation therapy 1. **Oral pain:** Radiation Therapy Oncology Group criteria (0 = none, 1 = mild at chewing, 2 = mild at rest, moderate at chewing, and unable to take hot, salty, or acidly tastes, 3 = moderate at rest, severe at chewing, and can drink liquid, 4 = severe pain and cannot take anything) 2. **Pain relief:** Rated at rest (i.e., no change, partial, complete, no response, and while eating)	**Severity of mucositis:** No significant differences in mucositis severity were found between the two groups. **Pain intensity:** No significant differences in pain intensity were found between the two groups. **Pain relief:** Significantly higher rates of complete pain relief at rest and while eating were reported in the AD film group. **Oral infections:** No secondary bacterial or fungal infections of the oral cavity or oropharynx were reported in AD film group.

Antiseptic Rinses

Two studies investigated the efficacy of prophylactic oral rinsing with an antiseptic agent: Adamietz et al. (1998) supplied participants (N = 38) with a povidone-iodine rinse, and Dudjak (1987) supplied participants (N = 15) with a hydrogen peroxide rinse. Topical application of povidone-iodine has good microbicide efficacy against bacteria, fungi, protozoa, and some viruses (Rahn et al., 1997). The effectiveness of hydrogen peroxide is the result of the enzymatic action of peroxidase in the chemical destruction of bacteria, as well as a deodorant effect because it oxidizes odorous gases. These two studies are summarized in Table 4.

Adamietz et al. (1998) conducted a clinical trial of 40 patients who were randomized to rinse either with a povidone-iodine solution or sterile water during the course of RT. The outcome measures included mucositis severity assessed using the World Health Organization (WHO) grading criteria (on a scale from 0–4): onset of mucositis, onset of grade 3 mucositis, maximal grading of mucositis, total duration of mucositis, and area under the curve (AUC) for grade versus duration. When compared with the control group, the povidone-iodine group had a significantly lower severity of mucositis (grade 1 versus grade 3) and a shorter duration of mucositis (2.8 weeks versus 9.3 weeks). Clinical manifestations of oral mucositis were observed in 14 patients in the treatment group (mean grade = 1) and in all 20 patients in the control group (mean grade = 3). The mean total duration of clinically observed mucositis was 2.75 weeks in the treatment group and 9.25 weeks in control group. Median AUC was 2.5 for the povidone-iodine group and 15.8 for the control group, which indicates that the treatment group experienced less severe mucositis during the course of RT. All differences found between the two groups were statistically significant ($p < 0.05$).

Dudjak (1987) randomized 15 patients to receive either a sodium bicarbonate rinse or a hydrogen peroxide solution to examine their effects on the physical condition of the mouth and on the patient's perception of oral comfort. A systematic oral hygiene protocol was offered to both groups. Severity of mucositis and the perception of symptoms associated with mucositis were the outcome measures. Both outcomes were measured using the Oral Examination Guide and the Oral Perception Guide developed by Beck (1979). No differences were found in the mean scores for the severity of mucositis at the completion of RT or one month later. However, patients who used the hydrogen peroxide rinse had significantly lower scores on the Oral Perception Guide, indicating higher levels of oral comfort ($p < 0.05$).

The results of the studies by Adamietz et al. (1998) and Dudjak (1987) need to be interpreted with caution. The limited number of studies and small sample sizes restrict the generalizability of the study findings. In addition, long-term use of a hydrogen peroxide rinse is discouraged because it may break down new granulation tissue and disrupt the normal oral flora

Table 4. Management of Radiation-Induced Mucositis With Antiseptic Agents

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Dudjak (1987)	Evaluate the difference in the physical condition of the oral mucosa and the individual's perception of comfort in patients receiving half-strength hydrogen peroxide (HP) versus sodium bicarbonate (SB) solution.	Randomized clinical trial (HP = 7, SB = 8)	**Objective:** Measured weekly and one month after radiation therapy **Mucositis severity:** Oral Examination Guide (Beck, 1979): Assessment of physical condition of mouth including regions of lips, mucous membranes, gingivae, saliva, ability to swallow, diet, self-care (1 = desirable condition to 4 = undesirable) **Subjective:** **Oral Perception Guide:** Patient perception of oral comfort regarding lips, gingivae, saliva, taste, eating (1 = desirable condition to 4 = undesirable)	**Mucositis:** No significant differences in the severity of mucositis were found between the two groups. **Perception of symptoms:** A significantly lower symptom perception score was found in the HP group at the completion of and at one month after radiation therapy ($p < 0.05$).
Adamietz et al. (1998)	Determine the efficacy of prophylactic povidone-iodine (P-I) mouth rinse in decreasing the severity of radiochemotherapy-induced mucositis.	Placebo-controlled, randomized clinical trial; standard prophylaxis for mucositis in both groups: nystatin, dexpanthenol, rutoside and immunoglobulins (P-I = 20, placebo = 20)	**Objective:** Measured every two weeks and at two and six weeks after radiation therapy 1. **Mucositis severity:** World Health Organization criteria (grade from 0–4) 2. **Onset of mucositis** 3. **Onset of grade 3 mucositis** 4. **Maximal grading** of mucositis 5. **Total duration** of mucositis 6. **Area under the curve** (AUC) for grade and duration: Severity and time curves	**Prevalence of mucositis:** Lower incidence of grade 3 mucositis was reported in the P-I group ($p < 0.05$). **Total duration of clinically observed mucositis:** Significantly shorter duration was observed in the P-I group ($p < 0.05$). **AUC median values:** Values were lower in the P-I group ($p < 0.05$).

because of its acidity (Barker, Loftus, Cuddy, & Barker, 1991). The clinical value of using povidone-iodine or hydrogen peroxide for reducing the severity of mucositis warrants further investigation.

Coating Agents

Coating agents have cytoprotective functions that facilitate mucosal healing and cell regeneration. The most common coating agent is sucralfate suspension. Sucralfate is a basic aluminum salt of sulphated sucrose that is used in the treatment of gastric and duodenal ulcers. When exposed to damaged mucosa, sucralfate creates a protective barrier by forming an ionic bond to proteins in the ulcer site (Verdi, 1993). Application of sucralfate to normal gastric tissues can cause rapid re-epithelialization of surface cells and an increase in the production of prostaglandin E2, a known cytoprotectant (Verdi). In addition, through the formation of a viscous coagulum, sucralfate may selectively coat areas of damaged mucosa and provide local protection from the effects of local irritants for several hours after application (Henriksson, Franzen, Edbom, & Littbrand, 1995). For these reasons, sucralfate was evaluated for use as an oral mucositis-modulating agent.

Eight double-blind, randomized clinical trials have investigated the efficacy of a sucralfate rinse in reducing RT-induced mucositis (see Table 5). The main outcome measures across the eight studies were the severity of mucositis, intensity of oral pain, and severity of various symptoms associated with mucositis (e.g., soreness, burning, dry mouth, dysphagia, difficulty eating). Seven studies demonstrated that no significant differences in the severity of mucositis, oral pain, or other associated symptoms existed when sucralfate suspension was compared to placebo (Barker et al., 1991; Carter et al., 1999; Epstein & Wong, 1994; Franzen, Henriksson, Littbrand, & Zackrisson, 1995; Lievens et al., 1998; Makkonen, Bostrom, Vilja, & Joensuu, 1994; Meredith et al., 1997). Only Cengiz et al. (1999) reported significantly less mucositis ($p < 0.05$) and significantly less pain during feeding ($p < 0.01$) when patients ($N = 28$) used sucralfate. The severity of mucositis was measured two times per week using the Radiation Therapy Oncology Group (RTOG) scale. In the other seven studies with nonsignificant findings, the severity of mucositis was evaluated only once a week. Therefore, the frequency with which the severity of mucositis is measured may be one confounding factor in the detection of changes in mucositis over time related to a specific treatment modality. However, Cengiz et al. failed to explain these positive findings in relation to seven negative trials.

One factor that needs to be considered when evaluating the findings from the sucralfate studies is the validity and reliability of the scales that were used to measure mucositis. Six of these studies developed a scale for the purposes of the study without testing the validity and reliability of the scale; two of the studies used the RTOG grading criteria. Most of the scales included only one item based on a 3- or 4-point Likert scale (i.e., none, mild, moderate, severe mucositis). In addition, none of these measures allowed for the assessment of the specific regions involved (e.g., tongue, buccal mucosa, gums) or

Table 5. Management of Radiation-Induced Mucositis With Sucralfate

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Barker et al. (1991)	Compare the efficacy of sucralfate suspension (1 g/15 ml three times a day) with the standard topical diphenhydramine syrup plus kaolin-pectin in alleviating radiation mucositis and pain.	Randomized clinical trial (sucralfate = 6, control = 6)	**Objective:** Measured weekly **Mucositis severity:** Based on a 0–3 scale (0 = none, 1 = erythema or burning sensation, 2 = erythema, pseudomembrane, or ulceration, pain, and patient capable of eating more than half of meals, 3 = erythema, pseudomembrane, or ulceration, and pain; patient unable to eat most of the time and less than half of meals) **Subjective:** Daily diary **Patient's self-perception of pain and helpfulness of mouthwash** on a 0–3 scale (0 = none, not helpful, 1 = slight pain, little help, relief for less than one hour; 2 = moderate pain, helpful, relief for one to two hours, 3 = extreme discomfort, very helpful, relief for two or more hours)	**Mucositis, perceived pain, and helpfulness of mouthwash:** No significant differences in any of the outcome measures were found between the two groups.
Epstein & Wong (1994)	Evaluate the efficacy of sucralfate suspension (1 g/5 ml four times a day) in the prevention of mucositis and relief of pain associated with radiation therapy involving the oropharyngeal region.	Double-blind, placebo-controlled, randomized clinical trial (sucralfate = 10, placebo = 17)	**Objective:** Measured weekly **Mucositis severity:** A score calculated by the product of the largest ulcer and the inflammation score (0 = none, 1 = mild, 2 = moderate, 3 = severe) for each of 10 regions of the oral cavity; a total score was obtained by adding the scores of 10 regions. **Subjective:** Measured weekly **Symptoms:** Visual Analog Scale of soreness, burning, dry mouth, pain (rest, eat, drink, speak, swallow)	**Mucositis:** No significant difference was found between the two groups. **Symptoms:** No significant differences were found in any of the symptoms assessed between the two groups. **Pain:** No significant difference in pain intensity was found between the two groups.
Makkonen et al. (1994)	Evaluate the efficacy of sucralfate mouthwash (1 g/100 ml six times a day) in the prevention and treatment of oral mucositis in patients irradiated to the oropharynx.	Double-blind, placebo-controlled, randomized clinical trial (sucralfate = 20, placebo = 20)	**Objective:** Measured at baseline, weekly, and one and six months after radiation therapy 1. **Mucositis severity:** 0–2 scale (0 = none, 1 = erythema, 2 = ulceration or bleeding, interfered with food intake or dental prosthesis) 2. **Salivary lactoferrin and albumin:** Markers for the severity of mucositis	**Mucositis severity:** No significant difference in the radiation therapy induced visible changes in the oral mucosa. **Salivary lactoferrin and albumin:** Significantly lower levels of salivary lactoferrin and albumin were found in the sucralfate group.
Franzen et al. (1995)	Test the effects of sucralfate (1 g six times a day) on the mucosal reactions to radiation therapy in the head and neck region.	Double-blind, placebo-controlled, randomized clinical trial (sucralfate = 28, placebo = 20)	**Objective:** Measured weekly **Mucositis severity:** 0–3 (0 = none, 1 = redness, 2 = redness and small areas of fibrinous epithelitis, 3 = confluent fibrinous epithelitis) **Subjective:** Daily patient self-report 1. **Pain:** Scored as 0 = none, 1 = mild, 2 = moderate, 3 = severe 2. **Functional impairment:** Problems with swallowing (0 = none, 1 = eat with slight difficulty, 2 = liquid or semisolid, 3 = needs nasogastric feeding)	**Mucositis:** Significantly greater severity of mucositis was found in the placebo group at weeks 1, 2, and 3 only ($p < 0.05$); no significant differences were found between groups from the third week after radiation therapy until the end of therapy. **Pain and functional impairment:** No significant differences in intensity of the two measures were found between the two groups.

(Continued on next page)

Table 5. Management of Radiation-Induced Mucositis With Sucralfate *(Continued)*

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Meredith et al. (1997)	Determine if sucralfate (3 g/30 ml four times a day) could provide improved symptomatic relief associated with radiation therapy-induced mucositis when added to a popular combination of antacid, diphenhydramine, and viscous lidocaine.	Double-blind, randomized clinical trial (sucralfate = 53, control = 58)	**Objective:** Measured weekly 1. **Mucositis severity:** On a scale of 0–3 (0 = none, 1 = erythema, 2 = less than 50% patchy mucositis, 3 = more than 50% patchy mucositis) 2. **Weight** **Subjective:** Measured weekly 1. **Ability to eat:** Graded on a 0–5 scale (0 = inability to eat a certain type of food to 5 = no compromise in the ability to ingest) 2. **Soreness:** Graded as 0–20, with 20 meaning most severe (unable to swallow secretions)	**Mucositis:** No significant difference in incidence of mild to moderate mucositis was found between the two groups. **Symptoms:** No significant differences in the severity of any of the subjective outcome measures were found between the two groups.
Lievens et al. (1998)	Test the possible effects of sucralfate (1 g six times a day) of reducing radiation therapy-induced acute mucositis.	Double-blind, placebo-controlled, randomized clinical trial (sucralfate = 45, placebo = 38)	**Objective:** Measured weekly 1. **Mucositis severity:** Graded on a 0–6 scale (0 = none, 1 = slight enanthema, 2 = deep enanthema, 3 = spotted mucositis less than 5 mm, 4 = spotted mucositis 5–10 mm, 5 = spotted mucositis greater than 10 mm, 6 = confluent mucositis) 2. **Weight** **Subjective:** Scored clinically once a week **Perception:** Subjective tolerance of radiation therapy, dysphagia, and nausea; on a scale of 0–4 with individual scoring criteria (0 = none to 4 = severe)	**Mucositis and subjective measures:** No statistically significant differences in the severity of mucositis and in any of the subjective outcome measures were found between the two groups.
Carter et al. (1999)	Determine whether sucralfate (1 g/15 ml four times/day) prophylaxis decreases symptoms resulting from mucositis during definitive radiation therapy for head and neck cancer and the impact of other patient- and treatment-related factors on symptoms.	Double-blind, placebo-controlled, randomized clinical trial (sucralfate = 50, placebo = 52)	**Objective:** Measured weekly 1. **Mucositis severity:** Radiation Therapy Oncology Group (RTOG) scoring criteria 2. **Weight** 3. **Time for mucositis healing** **Subjective:** Measured weekly 1. **Pain:** RTOG scoring criteria (0 = no discomfort, 1 = mild discomfort, no narcotics, 2 = moderate discomfort, no narcotics, 3 = severe, no narcotics, 4 = none or mild discomfort with narcotics, 5 = moderate discomfort despite narcotics, 6 = severe discomfort despite narcotics) 2. **Diet status:** Graded on a scale of 1–3 (1 = normal foods, 2 = soft foods, 3 = liquid only)	**Mucositis, weight, time for healing, pain, and diet status:** No significant differences were found in any of the objective or subjective outcome measures between the two groups.
Cengiz et al. (1999)	Test the efficacy of sucralfate (1.5 g four times a day) in the prevention and treatment of oropharyngeal mucositis and pain.	Double-blind, placebo-controlled, randomized clinical trial (sucralfate = 18, placebo = 10)	**Objective:** Measured twice a week **Mucositis severity:** RTOG scoring criteria **Subjective:** Measured twice weekly **Symptoms:** Steady oral pain, pain during feeding, dry mouth, alteration in taste, tolerable consistency of food, and constipation (no description of scoring)	**Mucositis:** Patients in the sucralfate group experienced a significant decrease in the severity of mucositis ($p < 0.05$). **Pain:** Patients in the sucralfate group reported significantly less during feeding ($p < 0.01$). **Symptoms:** No significant differences were found in any of the other subjective outcome measures.

for the size of the ulcer, which are critical factors to consider in any evaluation of the severity of mucositis. Another confounding factor in all of the sucralfate studies is the relatively small sample size, which ranged from 12–111.

The use of a sucralfate suspension rinse during RT did not reduce the severity of mucositis or decrease the level of pain according to the findings from seven of the eight clinical trials. However, numerous weaknesses across all of the studies including small sample sizes, the lack of valid and reliable measures of the severity of mucositis, and inconsistencies in the frequency of administration of the mouthwash make it impossible to draw definitive conclusions about the effectiveness of sucralfate in the management of RT-induced mucositis.

Anti-Inflammatory Rinsing Agents

Kamillosan liquidum rinse (Carl & Emrich, 1991), hydrocortisone rinse (Rothwell & Spektor, 1990), prostaglandin E1 rinse (Hanson, Marks, Reddy, Simon, & Mihalp, 1997), and oral corticosteroids (Leborgne, Leborgne, Zubizarreta, Ortega, & Mezzera, 1998) have been evaluated based on the hypothesis that these agents could decrease the inflammatory process, minimize microbial infection, or protect the oral mucosa from radiation damage. The four studies that used these agents are summarized in Table 6.

Rothwell and Spektor (1990) conducted a randomized clinical trial (N = 12) to compare the effectiveness of a mouthwash containing hydrocortisone, nystatin, tetracycline, and diphenhydramine to a cherry syrup containing sorbitol, magnesia and alumina suspension, and vitamins in controlling RT-related mucositis. The composition of the study rinse was devised to reduce the inflammation and microbial infection associated with RT-induced mucositis. The outcome measures in the study included the severity of mucositis and other symptoms associated with mucositis (e.g., pain, burning). These outcome measures were evaluated weekly using a 0–5 scale with 0 indicating no mucositis or symptoms and 5 indicating extremely severe mucositis or symptoms. Although a trend existed toward less intense symptoms and a decrease in the severity of mucositis in the group who received the anti-inflammatory antibiotic mouthwash, no significant differences were found in either measure between the two groups.

Carl and Emrich (1991) investigated the use of a kamillosan liquidum oral rinse in reducing or preventing the severity of RT-induced mucositis in a study of 20 patients with head and neck cancer. The findings were compared to a previous group of 20 patients who received conventional oral care with 5% sodium bicarbonate, saline, and 3% hydrogen peroxide. Severity of mucositis was graded on a 0–3 scale with 0 indicating no noticeable tissue change to 3 indicating confluent ulceration. Sixty-five percent of the patients who received the study mouthwash (n = 13) developed grade 2 mucositis (i.e., patchy ulceration) and 30% (n = 6) had grade 1 mucositis (i.e., erythema) at the end of RT. In the previous group who received conventional oral care, most patients progressed rapidly to grade 3 mucositis (i.e., confluent ulceration) by the end of RT.

Hanson et al. (1997) randomized 69 patients to receive either a prophylactic prostaglandin E1 mouth rinse or a placebo rinse during RT. The outcome measures included the severity of mucositis, weight change, the use of analgesics, and subjective perception of oral status. The severity of mucositis and the subjective perception of oral status were scored using a scale that ranged from 0–4 with 0 indicating no reaction to 4 indicating deep confluent membranous mucositis with severe ulceration. No significant differences were observed in any of the outcome measures between the two groups during RT.

Leborgne et al. (1998) conducted a randomized clinical trial with 66 patients to evaluate the efficacy of daily oral corticosteroids or a placebo in reducing the severity of RT-induced mucositis. The primary outcome measure was the severity of mucositis assessed using the WHO grading criteria. The secondary outcomes included treatment interruptions, degree and extent of mucositis, hospitalization, parenteral or nasogastric tube feeding, percentage of body weight loss, and long-term local control of the cancer and survival. No significant differences were found in the severity of mucositis or in any of the secondary outcomes between the two groups at the end of RT.

Although the use of anti-inflammatory agents to reduce the severity of mucositis makes sense from a mechanistic perspective, none of the studies conducted to date using these agents has produced significant results. All of these studies had extremely small sample sizes and used a single item to measure the severity of mucositis. Therefore, insufficient power and the lack of sensitivity of the outcome measures makes it difficult to draw definitive conclusions regarding the use of these agents with patients who are receiving RT to the head and neck region.

Cytokine-Like Agents

Cytokine-like agents (e.g., granulocyte macrophage colony-stimulating factor [GM-CSF]) or human immunoglobulin in a mouth rinse or subcutaneously enhance the proliferation of endothelial cells and keratinocytes in the basal epithelium (Biron et al., 2000). To date, six studies have investigated the efficacy of GM-CSF or immunoglobulin in managing RT-induced mucositis (see Table 7).

Granulocyte Macrophage Colony-Stimulating Factor

GM-CSF is a glycoprotein, a potent growth factor for the myeloid lineage of hematopoietic cells. GM-CSF not only enhances colony formation of granulocytes and macrophages, but it also regulates several functions of mature leukocytes and macrophages in the dermis and submucosa leading to increased production of antibodies and increased phagocytic activity (Bapsy, Doval, Kannan, & Anantha, 1995; Makkonen et al., 2000). GM-CSF is known to enhance keratinocyte and fibroblast growth, which are essential in wound healing, namely in the regeneration of parenchymal cells and connective tissue, collagen formation, and acquisition of wound tissue strength (Makkonen et al., 2000). These properties may contribute to a reduction in the severity of mucositis and an acceleration of the healing process in RT-induced mucositis.

Subcutaneous granulocyte macrophage colony-stimulating factor: Kannan et al. (1997) studied 10 patients who received daily subcutaneous injections of GM-CSF (1 *m*g/kg) from the time that they had received 20 Gy of irradiation until the end of RT. Rosso, Blasi, Gherlone, and Rosso (1997) evaluated the efficacy of subcutaneous GM-CSF in a sample of 29 patients. Patients received a daily subcutaneous injection (5 *m*g/kg) from the beginning of RT, as well as five days

Table 6. Management of Radiation-Induced Mucositis With Anti-Inflammatory Rinsing Agents

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Rothwell & Spektor (1990)	Compare the effectiveness of hydrocortisone, nystatin, tetracycline, and diphenhydramine to a cherry syrup containing sorbitol, magnesia and alumina suspension, and vitamins in controlling radiation therapy-related mucositis.	Double-blind, randomized clinical trial (hydrocortisone = 5, control = 7)	**Objective:** Measured weekly **Mucositis severity:** Erythema, mucositis, ulceration, and moniliasis on a scale of 0–5 (0 = no difficulty to 5 = patient experienced extreme difficulty) **Subjective:** Measured weekly **Symptoms, pain, and burning:** Related to oral mucosa and saliva on a scale of 0–5 (0 = no symptoms to 5 = patient experienced extreme difficulty)	**Mucositis and symptoms:** The experimental group developed less severe mucositis and had fewer patient-reported symptoms between weeks 4–6 of radiation therapy ($p < 0.01$).
Carl & Emrich (1991)	Determine if specific oral care with a kamillosan liquidum oral rinse would reduce and/or prevent the severity of radiation therapy-induced mucositis.	Compared 20 patients who received kamillosan prophylaxis to a previous group who did not receive kamillosan (sample not described)	**Objective:** Measured weekly **Mucositis severity:** Tissue changes recorded on a scale of 0–3 (0 = no clinically noticeable tissue change, 1 = erythema, 2 = surface desquamation in disconnected islands smaller than 1 cm in size, 3 = large confluent areas of surface ulcerations)	**Mucositis:** Most patients developed grade 1 or 2 mucositis at the end of radiation therapy compared to a previous group who received a similar dose of radiation and conventional oral care without using kamillosan who developed grade 3 mucositis.
Hanson et al. (1997)	Test the efficacy of prostaglandin E1 mouth rinse to directly protect the oral mucosa from some degree of injury and thereby reduce radiomucositis.	Double-blind, placebo-controlled, randomized clinical trial (prostaglandin E1 = 34, control = 35)	**Objective:** Measured weekly 1. **Mucositis severity:** On a scale of 0–4 (0 = no reaction, 1 = mild to moderate erythema, 2 = patchy membranous mucositis with mild ulceration, 3 = ulceration without confluent mucositis, 4 = deep confluent mucositis with severe ulceration) 2. **Weight** 3. **Analgesic use** **Subjective:** Measured weekly patient perception of oral status; grading criteria used the same scale for mucositis severity	**Mucositis:** No significant differences were found between the two groups. **Weight loss, analgesic use, perception of oral status:** No significant differences were found between the two groups.
Leborgne et al. (1998)	Test the efficacy of oral corticosteroids on remodeling mucosal cell depletion and repopulation associated with radiation therapy-induced mucositis.	Double-blind, placebo-controlled, randomized clinical trial (corticosteroid = 32, placebo = 34)	**Objective:** 1. **Mucositis severity:** World Health Organization criteria, confluence and duration of ulceration 2. **Secondary outcomes:** Treatment interruptions, degree and extent of mucositis, hospitalization, parenteral or nasogastric feeding, percentage of body weight loss, and long-term local control and survival	**Mucositis:** No significant differences in the intensity or duration of mucositis were found between the two groups. **Secondary outcomes:** Less weight loss ($p = 0.02$) was reported in the corticosteroid group; no significant differences in any of the other outcomes were found between the two groups.

following the last chemotherapy treatment. Makkonen et al. (2000) conducted a randomized clinical trial comparing subcutaneous GM-CSF (150–300 *m*g/day) plus sucralfate mouthwash to sucralfate mouthwash alone in the prevention of RT-induced mucositis. The main outcome measures in these studies were the severity of mucositis and pain intensity, which were measured either daily (Makkonen et al., 2000) or weekly (Kannan et al.; Rosso et al.).

Most patients in the three studies completed RT or radiochemotherapy with only grade 1 (i.e., erythema) or grade 2 mucositis (i.e., patchy mucositis in less than half of the irradiated field or ulcerations with a bleeding mucosa). Most of the patients had mild pain and were able to tolerate oral intake. The reported toxicities associated with subcutaneous GM-CSF included skin reactions at the GM-CSF injection site, body aches, bone pain, or fever (Kannan et al., 1997; Makkonen et al., 2000; Rosso et al., 1997).

Although the findings from the three pilot studies with subcutaneous GM-CSF suggested that this approach might prove beneficial in patients receiving RT or chemotherapy for head

Table 7. Management of Radiation-Induced Mucositis With Cytokines

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Kannan et al. (1997)	Determine the safety and mucosal reaction of patients who received prophylaxis with subcutaneous granulocyte macrophage colony-stimulating factor (GM-CSF) during conventional fractionated radiation therapy in patients with head and neck cancer.	Descriptive pilot study. Daily GM-CSF was given subcutaneously at a dose of 1 μg/kg body weight after 20 Gy of irradiation until the completion of radiation therapy (N = 10).	**Objective:** Measured daily **Mucositis severity:** On a scale of 0–4 (0 = none, 1 = erythema, 2 = patchy mucositis less than 50%, 3 = patchy mucositis more than 50%, 4 = confluent mucositis) **Subjective:** Measured daily 1. **Pain:** On a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) 2. **Functional/eating impairment:** On a scale of 0–3 (0 = none, 1 = able to eat with slight difficulty, 2 = able to take semisolids, 3 = able to drink liquid only, 4 = tube feeding)	**Mucositis:** All patients developed grade 1 or 2 mucositis at the end of radiation therapy. **Pain:** Most patients experienced no or grade 1 oral pain at the end of radiation therapy. **Functional impairment:** Most patients were able to eat only semisolid food (grade 2 eating impairment) at the end of radiation therapy. **Side effects:** Two patients had skin reactions and four others had body aches; two requested stopping radiation therapy and GM-CSF administration.
Mose et al. (1997)	Determine the effect of prophylactic intramuscular weekly injection of immunoglobulin on the degree of mucositis and on the frequency of radiation therapy or radiochemotherapy interruptions.	Descriptive comparative study. The first 20 patients received only prophylactic mouthwash (panthenol and nystatin). The next 22 patients received mouthwash plus intramuscular immunoglobulin (800 mg) weekly until the end of radiation therapy.	**Objective:** Examined three times weekly 1. **Mucositis severity:** Radiation Therapy Oncology Group criteria (grade 0–4) 2. **Onset of mucositis:** Days 3. **Radiation therapy interruptions** because of intolerable mucositis pain **Subjective:** Daily patient self-report 1. **Symptoms:** Xerostomia and dysphagia 2. **Side effects:** Associated with immunoglobulin use	**Mucositis:** Trend for more severe mucositis was seen in the control group; degree of maximum mucositis was significantly less in the immunoglobulin group. **Onset of mucositis and radiation therapy interruptions and symptoms:** No significant differences were reported in the above measures between the two groups. **Side effects:** Six patients reported local burning in the oral mucosa associated with immunoglobulin.
Rosso et al. (1997)	Evaluate in an open trial the efficacy of GM-CSF on the rate and severity of mucositis produced by a therapeutic program of alternating chemotherapy and radiation in patients with inoperable squamous cell carcinoma of the head and neck.	Descriptive study. GM-CSF was given to 29 patients at a dose of 5 μg/kg subcutaneously on the days when radiation therapy was given and for five days following the last chemotherapy.	**Objective:** Measured weekly **Mucositis severity:** World Health Organization scoring criteria (scale from 0–4) **Subjective:** Measured weekly **Symptoms:** Pain, eating function, and other local or systemic symptoms based on self-administered questionnaire (no further description of the grading criteria)	**Mucositis:** Most patients developed grade 1 and 2 mucositis during radiation therapy. **Symptoms:** Results were not reported.
Nicolatou et al. (1998)	Evaluate the effect of GM-CSF mouth rinse in reducing radiation therapy-induced oral mucositis for head and neck cancer.	Descriptive study. After patients complained of oral pain, a GM-CSF mouthwash (400 μg in 200 ml of drinking water) was administered daily until the end of radiation therapy (N = 17). Patients were asked to swish and gargle the 200 ml mouthwash in fragments within one hour.	**Objective:** Measured weekly **Mucositis severity:** 0 = none, 1 = erythema, 2 = small ulcers, 3 = covered by pseudomembrane more than 50% of mucosa, 4 = necrotic ulcers and hemorrhage **Subjective:** Measured weekly **Functional impairment:** 0 = none, 1 = mild soreness, solid diet, 2 = mild to moderate pain, soft diet, 3 = severe pain, dysphagia, and liquid only, 4 = severe, parental support	**Mucositis and functional impairment:** Most patients developed grade 1 mucositis at the end of radiation therapy. **Interruption of radiation therapy:** Most patients completed radiation therapy without interruptions (only one patient had a two-day interruption). **Discontinuation of radiation therapy:** One patient discontinued radiation therapy at third week because of grade 4 mucositis aggravated by an extensive gold prosthesis.

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Table 7. Management of Radiation-Induced Mucositis With Cytokines *(Continued)*

Author	Study Purpose	Research Design (N)	Outcome Measures	Findings
Rovirosa et al. (1998)	Evaluate the effectiveness of GM-CSF mouthwash in managing radiation therapy-induced oral mucosal ulceration, control of pain, and weight loss.	Case-control study. Daily GM-CSF mouthwash (300 *m*g in 250 ml of drinking water) given to patients (N = 12) who experienced grade 1 mucositis. Patients were asked to swish without swallowing with the 250 ml mouthwash within one hour. Results were compared to 12 retrospective case-matched controls.	**Objective:** Measured twice per week 1. **Mucositis severity:** World Health Organization criteria (0 = none, 1 = soreness, erythema, 2 = erythema, ulcers, solid food, 3 = ulcers, liquid diet only, 4 = hemorragia, oral intake not possible) 2. **Weight** **Subjective:** **Pain:** No description of measures	**Mucositis:** Less severe mucositis was reported in most patients of the GM-CSF group (grade 1/2 compared to 3/4 in case control group). **Pain:** Pain intensity decreased in GM-CSF group; 50% of patients reported decreased pain and 30% needed morphine in GM-CSF group; 92% of patients reported increased pain and 60% needed morphine in control group. **Weight loss:** Less weight loss was reported in GM-CSF group (4.2% of baseline compared to 5.8% in case-control group).
Makkonen et al. (2000)	Compare the effectiveness of subcutaneous GM-CSF and sucralfate rinse to sucralfate alone in preventing radiation therapy-induced mucositis.	Randomized clinical trial. After a cumulative radiation dose of 10 Gy, 20 patients were given daily subcutaneous GM-CSF (150 *m*g for patients less than 70 kg and 300 *m*g for patients more than 70 kg) in addition to sucralfate rinse. Twenty patients received only the sucralfate rinse.	**Objective:** Measured weekly 1. **Mucositis severity:** Graded on a 0–2 scale (0 = none, 1 = moderate erythema, 2 = severe ulceration, bleeding, interference with food intake) 2. **Salivary lactoferrin:** Mucositis marker 3. **Weight** **Subjective:** Measured weekly 1. **Oral pain:** Clinician was graded on a 1–4 scale: (1 = none, 2 = mild, 3 = moderate, 4 = severe); patient was graded on a Visual Analog Scale of 0–10.	**Mucositis:** No significant differences were found in the severity of mucositis (63% patients with grade 2). **Salivary lactoferrin:** A higher level was found in GM-CSF group ($p < 0.01$). **Pain and weight loss:** No significant differences in pain intensity and weight loss were found between the two groups. **Side effects:** Four patients had interruptions of treatment because of side effects associated with GM-CSF (e.g., local skin reaction, fever, bone pain, nausea).

and neck cancer, the results of Makkonen et al.'s (2000) randomized clinical trial were rather disappointing in that no significant differences were found in the severity of mucositis or pain between the two groups. In addition, the drop-out rate in the GM-CSF group was 25% as a result of intolerable side effects of GM-CSF. However, all three studies had extremely small sample sizes. In addition, the scales used to measure the severity of mucositis may not have been sensitive enough to detect changes over time. Finally, the dose of GM-CSF varied 30-fold across these studies making it impossible to determine whether this approach has any role in the management of RT-induced mucositis.

Granulocyte macrophage colony-stimulating factor mouthwash: Nicolatou et al. (1998) studied the use of a GM-CSF mouth rinse (400 *m*g in 200 ml of drinking water) in 17 patients who used the mouthwash from the second week of RT until the end of RT. Rovirosa, Ferre, and Biete (1998) evaluated the efficacy of using GM-CSF mouthwash (300 *m*g in 250 ml of drinking water) in 12 patients and compared the results to 12 retrospective case-matched controls. The outcome measures used in both studies were the severity of mucositis and associated oral pain. The severity of mucositis was graded using a 0–4 scale with 4 indicating a confluent mucositis or necrotic hemorrhage.

Most patients in both studies had a grade 1 or 2 mucositis at the end of RT without any treatment interruptions. In contrast, most patients in the case-control group, who performed conventional mouth care, progressed to a grade 3 or 4 mucositis at the end of RT. All patients who used the GM-CSF mouthwash experienced grade 3 pain (i.e., severe pain) and were able to take semisolid food or liquid diet (Nicolatou et al., 1998). Fifty percent of the patients who used GM-CSF mouthwash experienced a decrease in oral pain compared to 92% of patients who used the conventional mouth care and experienced an increase in pain (Rovirosa et al., 1998). A lower percentage of patients in the GM-CSF group required morphine than in the case-control group (30% versus 60%) (Rovirosa et al.).

Although only these two studies have evaluated the use of a GM-CSF mouthwash in preventing RT-induced mucositis, the results suggest that this approach may provide some therapeutic benefit to patients with head and neck cancer. Additional studies using this approach are warranted.

Immunoglobulin

The mechanism of action of immunoglobulin on the oral mucosa is not well understood. Prophylactic and therapeutic application of immunoglobulin has been hypothesized to induce local inflammatory mucosal reactions and increase local

immune defenses. Immunoglobulin also may activate quantitative and qualitative changes in T cells to further stimulate the immune system that can be suppressed from the cancer treatment (Mose et al., 1997).

Only Mose et al. (1997) have investigated the effect of prophylactic intramuscular injection of immunoglobulin in the management of RT-induced mucositis. A standard prophylactic treatment for mucositis that consisted of panthenol and nystatin was given to all patients as prophylaxis. The first 20 consecutive patients received the standard prophylactic treatment, whereas the subsequent 22 patients received supplementary intramuscular injections of human immunoglobulin every week until the end of RT. The severity of mucositis was evaluated using the RTOG grading criteria. The mean degree of maximum mucositis in the immunoglobulin group was significantly less than in the control group (1.9 versus 2.6, $p = 0.031$) in those patients who received combined treatment of RT and chemotherapy. However, no differences in the severity of mucositis were found between the two groups when the patients were treated with RT alone. Therefore, definitive conclusions cannot be drawn about the efficacy of immunoglobulin in the management of RT-induced mucositis until additional studies are performed.

Conclusion

Oral mucositis is the most common complication among patients with head and neck cancer who are treated with RT or chemotherapy. This risk increases with the intensification of the radiation dose, treatment schedules, or use of combined modality treatments (i.e., surgery, RT, or chemotherapy). The prevention of mucositis or a reduction in morbidity associated with mucositis is a highly desirable goal for patients who are receiving treatment for head and neck cancer.

Although a number of strategies and products are being investigated and new directions are promising, many of them do not produce consistent results. The most effective measure to treat RT-induced mucositis is frequent oral rising with a bland mouthwash, such as saline or a sodium bicarbonate rinse, to reduce the amount of oral microbial flora (Symonds, 1998). Consistent oral care can ensure the elimination of acute and potential dental and periodontal foci of pathologic conditions before cancer treatment is started (Biron et al., 2000). Therefore, dental care, consistent oral assessments, and the initiation of a standardized oral hygiene program before cancer treatment is initiated most often is the suggested approach to provide the optimal efficacy in managing oral mucositis (Biron et al.; Dodd et al., 1996; Dudjak, 1987; Graham, Pecoraro, Ventura, & Meyer, 1993; National Cancer Institute, 2000; Scully & Epstein, 1996; Symonds).

Pathophysiologically specific treatment remains a controversial area. Significant limitations in study designs and lack of consistency in measurement approaches make comparisons of studies of antimicrobials, coating agents, and anti-inflammatory agents difficult. This area is in need of further investigation. Research findings suggest that a particularly promising approach is the use of cytokines (e.g., GM-CSF) that may facilitate epithelial healing and maturation during RT. However, the management of the other morbidities associated with oral mucositis (i.e., oral pain relief, nutritional needs, inhibition of oral microflora) still is the main goal of care for patients with head and neck cancer who receive RT. Further research is needed to address these significant concomitant morbidities. Last but not least, the development of a well-defined scoring system that can provide more sensitive measurement of the severity and duration of mucositis is important to all disciplines involved in the field of studying RT-induced mucositis.

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