Putting Evidence Into Practice®: Evidence-Based Interventions for the Management of Oral Mucositis

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Mucositis, an inflammation of the mucous membranes, is a commonly occurring side effect of chemotherapy and radiation. Oral mucositis can cause significant clinical consequences, such as pain, malnutrition, and local and systemic infections. Nurses have a critical role in all aspects of managing mucositis, including assessing it, teaching oral care, administering pharmacologic interventions, and helping patients cope with symptom distress. Mucositis can have a negative impact on the overall treatment experience, especially when severe pain or infections occur. Many interventions for managing mucositis exist; however, some are based in tradition or expert opinion and have not been studied in large, randomized, controlled trials. In addition, a variety of assessment tools are available, which creates confusion and difficulties when comparing interventions across studies. This article reviews empirical evidence related to interventions for oral mucositis. Oral care and rinses, pharmacologic interventions, and other techniques are evaluated. Gaps in the literature and opportunities for research, education, and practice changes are discussed.

Nursing-sensitive patient outcomes are outcomes that are attained through or significantly impacted by nursing interventions. The interventions must be within the scope of nursing practice and integral to the process of nursing care.

Mucositis is a general term that describes the inflammatory response of mucosal epithelial cells to the cytotoxic effects of chemotherapy and radiation therapy. All mucous membrane–covered surfaces from the mouth to the rectum may be affected (Wojtaszek, 2000). Oral mucositis disrupts the function and integrity of the oral cavity, which, in turn, affects functional status and quality of life. It is associated with significant clinical morbidity, which may include pain, malnutrition, and local and systemic infections (Eilers, 2004). Treatment delays and dosage adjustments also can occur. The incidence and severity of mucositis vary among patient populations; however, mucositis can have a significant impact on treatment outcomes and quality of life in patients receiving mucotoxic therapy for cancer.

Although present throughout the gastrointestinal tract, mucositis in the oral cavity is studied more frequently and better characterized in the literature because of the ease of assessment. The mucositis Oncology Nursing Society Putting Evidence Into Practice® (PEP) group chose to examine interventions for the management of oral rather than gastrointestinal mucositis because of the greater breadth and more extensive literature in this area. Because mucositis is a systemic process, interventions with the greatest impact are those that exert their effects systemically.

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Methods

The team searched MEDLINE®, the U.S. National Library of Medicine's bibliographic database, CINAHL® (Cumulative Index to Nursing and Allied Health Literature) and CCRCT (Cochrane Central Register of Controlled Trials). Searches explored the terms *neoplasms for nursing, prevention and control, diet therapy, drug therapy, radiotherapy, surgery,* and *therapy.* Other search terms included *mucositis, stomatitis, mucous membrane, radiotherapy,* and *antineoplastic agents.* A health services librarian was consulted to review the search terms and strategy. The literature search included citations from 2000 to September 2006. Sources cited before 2000 were reviewed as appropriate.

Highlights of Reviewed Literature

Interventions have been applied to the appropriate level of evidence based the ONS PEP Weight-of-Evidence Classification Schema. See Table 1 for a description of this schema.

Recommended for Practice

Oral care is widely considered the foundation of mucosal health, integrity, and function; however, the specific components, methods, and frequency of oral care remain in dispute, partly because of the ethical considerations of withholding oral care in clinical trials. The literature does state that **oral care protocols** help to minimize the effects of oral mucositis in patients receiving treatment for cancer (Rubenstein et al., 2004). Oral care can reduce the amount of microbial flora, reduce pain and bleeding, and prevent infection. Good oral health also reduces the risk of dental complications (Cawley & Benson, 2005; Rubenstein et al.). Although oral care has not been demonstrated to prevent mucositis, adherence to a regimen can reduce the duration and severity of mucositis (McGuire, Correa, Johnson, & Wienandts, 2006; Rubenstein et al.). The review of the literature indicated that a systematic approach to oral care should be followed. The focus of oral care protocols is not on specific agents, but on feasibility, adherence, and patient education. The protocol also may be specific to patients' diagnosis and treatment (Rubenstein et al.).

The basic components of an oral care protocol include assessment, patient education, tooth brushing, flossing, and oral rinses. A multidisciplinary, collaborative team approach is important for implementation of the protocol. Figure 1 includes a minimum of recommended oral care components. Oral assessment, using a validated tool, also should be conducted regularly to assess function, pain, and the oral mucosa. The participation of a dentist is recommended throughout treatment and follow-up (Multinational Association of Supportive Care in Cancer [MASCC], 2005). Bland rinses, recognized as an important part of oral hygiene, have not been studied adequately to meet the criteria for the Recommended for Practice category. They are included under Expert Opinion later in this article.

To date, few studies have addressed the superiority of different oral care regimens. As a result, the detailed components of oral care protocols currently meet the criteria for expert opinion.

Table 1. Putting Evidence Into Practice® Weight-of-Evidence Classification Schema

WEIGHT-OF-EVIDENCE CATEGORY	DESCRIPTION	EXAMPLES
Recommended for practice	Effectiveness is demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews. Expected benefit exceeds expected harms.	At least two multisite, well-conducted, randomized, controlled trials (RCTs) with at least 100 subjects Panel of expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence
Likely to be effective	Evidence is less well established than for those listed under recommended for practice.	One well-conducted RCT with fewer than 100 patients or at one or more study sites Guidelines developed by consensus or expert opinion without synthesis or quality rating
Benefits balanced with harms	Clinicians and patients should weigh the beneficial and harmful effects according to individual circumstances and priorities.	RCTs, meta-analyses, or systematic reviews with documented adverse effects in certain populations
Effectiveness not established	Data currently are insufficient or are of inadequate quality.	Well-conducted case control study or poorly controlled RCT Conflicting evidence or statistically insignificant results
Effectiveness unlikely	Lack of effectiveness is less well established than those listed under not recommended for practice.	Single RCT with at least 100 subjects that showed no benefit No benefit and unacceptable toxicities found in observational or experimental studies
Not recommended for practice	Ineffectiveness or harm clearly is demonstrated, or cost or burden exceeds potential benefit.	No benefit or excess costs or burden from at least two multisite, well-conducted RCTs with at least 100 subjects Discouraged by expert recommendation derived from explicit literature search strategy; includes thorough analysis, quality rating, and synthesis of evidence

Note. Based on information from Mitchell & Friese, n.d.

Clinicians

- Collaborate with a multidisciplinary team in all phases of treatment.
- Conduct a systematic assessment at least daily or at each patient visit. In the outpatient setting, teach patients to perform oral assessment daily. Teach patients when to report findings to the clinician.
- Provide written instruction and education to patients regarding oral care. Verify understanding with return explanation and demonstration.

Patients

- Brush all tooth surfaces for at least 90 seconds, twice daily using a soft toothbrush. Allow toothbrush to air dry before storing. Replace toothbrush on a regular basis.
- Floss at least once daily or as advised by the clinician.
- Rinse mouth four times daily with a bland rinse.
- Avoid tobacco, alcohol, or irritating foods (acidic, hot, rough, spicy).
- Use water-based moisturizers to protect lips.
- Maintain adequate hydration.

Figure 1. Core Elements of an Oral Care Protocol

Note. Based on information from Dodd et al., 2000; Eilers, 2004; Kwong, 2004; Multinational Association of Supportive Care in Cancer, 2005; Rubenstein et al., 2004; Scully et al., 2006; Shih et al., 2002.

Two studies in the pediatric setting have demonstrated the superiority of using protocols over general oral care. One study (N = 42) found a preventive oral care protocol consisting of patient education and instruction on tooth brushing and use of rinses effectively reduced oral mucositis in children with cancer. The control group consisted of children who did not receive the oral care protocol or information about oral care. The incidence of mucositis in the oral protocol group decreased by 38% compared to the children in the control group. The severity of pain and the severity of oral mucositis also were significantly reduced (Cheng, Molassiotis, Chang, Wai, & Cheung, 2001).

The second pediatric study (N = 40) compared three oral care protocols: tooth brushing, normal saline rinse, and chlorhexidine or benzydamine rinses. No significant differences in oral mucositis were found between protocols. The results of this study did not demonstrate superiority of a specific rinse, but rather, reinforced the importance of oral care (Cheng, Chang, & Yuen, 2004).

A third study compared salt and sodium bicarbonate (one teaspoon each of salt and sodium bicarbonate per pint of water) rinses, chlorhexadine and "magic" mouthwash (5 ml 0.5% lidocaine, 0.25 ml 0.0312% diphenhydramine, and 14.75 ml aluminum hydroxide/magnesium hydroxide) in adult patients receiving chemotherapy. The results of this randomized study (N = 142) did not show any significant difference for average number of days to mucositis resolution or pain scores. The similarity in the results for the three groups indicates the benefits of a systematic oral care protocol. These results also support the use of the inexpensive salt and sodium bicarbonate rinse (Dodd et al., 2000) as the other rinses are more expensive and may contain alcohol or other irritating ingredients.

Cryotherapy involves the use of ice chips or ice cold water for the prevention of oral mucositis. Patients suck on ice or hold ice cold water in their mouths prior to, during, and after rapid infusions of mucotoxic agents with a short half-life. Cryotherapy is based on the theory that vasoconstriction decreases exposure of the oral cavity mucous membranes to the mucotoxic agents (Lilleby et al., 2006, Mori et al., 2006, Nikoletti, Hyde, Shaw, Myers, & Kristjanson, 2005; Tartarone, Matera, Romano, Vigliotti, & Di Renzo, 2005).

Use of cryotherapy for bolus 5-fluorouracil (5-FU) is supported in the MASCC (2005) guidelines and a Cochrane Review of interventions for the prevention of oral mucositis (Worthington, Clarkson, & Eden, 2004). In addition, studies have provided support for the use of cryotherapy with high-dose melphalan (Lilleby et al., 2006, Mori et al., 2006). Reviews by Eilers (2004); Kwong (2004); Migliorati, Oberle-Edwards, and Schubert (2006); and Scully, Sonis, and Diz (2006) also recommended the use of cryotherapy, with those selected agents. Effectiveness is limited to chemotherapy agents with a short half-life and the majority of the evidence to date is for 5-FU and high-dose melphalan. Other agents that have been studied, but lack adequate evidence to make a recommendation regarding cryotherapy, include etoposide, platinol, mitomycin, edatrexate, and vinblastine (Karagozoglu & Ulusoy, 2005).

The optimum duration and intensity of cryotherapy requires further systematic investigation. Studies to date have been inconsistent as has documentation regarding patient adherence to the cooling protocol. Based on current knowledge, patients should hold ice or ice cold water in their mouths for at least five minutes prior to the infusion, during the infusion, and for 30 minutes after completion of the infusion. Individuals who do not tolerate cold in their oral cavity do not tolerate cryotherapy well. In addition, cryotherapy is not indicated with chemotherapy agents such as oxaliplatin, which are known to result in potential problems with exposure to cold. Oxaliplatin is associated with acute neurologic symptoms, including jaw tightness and laryngopharyngeal dysesthesia, which often occur after exposure to cold (Fischer, Knobf, Durivage, & Beaulieu, 2003).

Palifermin is a recombinant human keratinocyte growth factor that stimulates growth of epithelial cells. This drug has been shown to reduce severity and duration of mucositis in patients with hematologic malignancies receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation (Spielberger et al., 2004). Palifermin is administered at a dose of 60 ug/kg per day via IV for three days prior to the beginning of the conditioning regimen and for three days after transplantation for the prevention of oral mucositis. Because of the high cost of this agent, it should be used for patients most likely to develop severe mucositis. The cost-effectiveness of palifermin and its use with specific conditioning regimens continue to be investigated. The most common side effects include mild rash and taste changes. Other adverse effects include pruritis, erythema, cough, edema, white coating of mouth or tongue, rhinitis, arthralgia, numbness, and paresthesia. These effects are mild to moderate, last approximately three days, and did not cause discontinuation of the drug in studies (MASCC, 2005; Scully et al., 2006; Spielberger et al.; von Bultzingslowen et al., 2006).

Effectiveness Not Established

Most of the agents examined in the review of literature were assigned to this category because of lack of clinical trials, inadequate sample size, methodological flaws, or conflicting evidence.

Antimicrobial agents: A wide variety of antimicrobial agents, including polymyxin, tobramycin, amphotericin B, fluconazole, and protegrin have been studied in several doses and combinations. No clear pattern of benefit has emerged, and little evidence exists to recommend the use of these agents (Donnelly, Bellm, Epstein, Sonis, & Symonds, 2003). One large (N = 275) placebo-controlled randomized trial has shown narrow-spectrum antibacterial lozenges to be effective for patients with head and neck cancer undergoing radiation (Scully et al., 2006). These agents may be costly, however, and the lack of effectiveness highlights the multifactorial pathophysiology of oral mucositis.

Benzydamine hydrogen chloride is a nonsteroidal drug with analgesic, anesthetic, anti-inflammatory, and antimicrobial properties that currently is used in Europe and Canada, but is not approved by the U.S. Food and Drug Administration. In one trial (N = 172), benzydamine produced a significant reduction ($p = 0.009$) in mucositis compared with placebo in patients receiving 0–5,000 cGy of radiation for head and neck cancer. Patients rinse with 15 ml of benzydamine for two minutes four to eight times daily before and during radiation therapy and for two weeks after completion of the course of radiation (Epstein et al. 2001). Those findings need to be replicated in additional large trials to determine benefit, dosage, and administration method (Scully et al., 2006; Worthington et al., 2004).

Growth factors and cytokines: Subcutaneous growth factors such as granulocyte–colony-stimulating factor and granulocyte macrophage–colony-stimulating factor (GM-CSF) promote neutrophil development in the bone marrow and also may have effects in the submucosa (Kwong, 2004; Shih, Miaskowski, Dodd, Stotts, & MacPhail, 2002). Studies with those agents have shown conflicting results, however, which may be because of inadequate sample sizes and variations in dose. Repifermin and velafermin are growth factors that are currently in clinical trials for mucositis (Freytes et al., 2004; Schuster et al., 2005).

Other Interventions

Allopurinol is believed to inhibit enzymes involved in the formation of toxic 5-FU metabolites. Although initial small trials found some positive findings using allopurinol mouthwash, those results were not confirmed in controlled trials (Kwong, 2004; Rubenstein et al., 2004; Scully et al., 2006). **Amifostine** functions as a free radical scavenger. Although amifostine is effective for prevention of acute and late xerostomia in patients with head and neck during standard fractionated radiotherapy, it has not shown beneficial effects for management of mucositis. Multiple studies have failed to demonstrate significant effects for duration or severity of mucositis (Bensadoun, Schubert, Lalla, & Keefe, 2006; MASCC, 2005). Because of poor study design and inadequate sample size, **anti-inflammatory rinses** with ingredients such as kamillosan liquidum, hydrocortisone, prostaglandin E1, and oral corticosteroids are included in the Effectiveness Not Established category (Shih et al., 2002). **L-alanyl-L-glutamine** is a stable glutamine derivative that has been shown to decrease 5-FU–induced mucositis in animals and humans. Studies with the agent have produced weak results to date (Cerchietti et al., 2006; MASCC). **Low-level laser therapy (LLLT)** is a promising intervention that may prevent, treat, and provide pain control for mucositis with little or no toxicity (Genot & Klastersky, 2005; Migliorati et al., 2006; Nes & Posso, 2005). Laser therapy does require special equipment and training that is not widely available. Rubenstein et al. (2004) suggested using LLLT where available to reduce the incidence of oral mucositis and associated pain in patients receiving chemotherapy or chemoradiation before hematopoietic stem cell transplantation.

Multi-agent ("magic" or "miracle") rinses include a variety of ingredients but typically contain lidocaine, diphenhydramine, and Maalox® (Novartis). As indicated previously, studies with these agents have not demonstrated their superiority over bland rinses to treat mucositis or alleviate pain. Concern that the numbing effect creates a potential for injury or difficulty swallowing exists. Formulations of those agents may contain alcohol, which should be avoided (Eilers, 2004). **Zinc** supplementation has been shown to delay the development and speed recovery of mucositis in one small trial (N = 30) and one larger trial (N = 97). The optimal dose has not been determined (Ertekin, Koc, Karslioglu, & Sezen, 2004; Lin, Que, Lin, & Lin, 2006).

Effectiveness Unlikely

Iseganan is an oral antimicrobial agent provided as an oral rinse. Two multisite, randomized controlled trials were conducted with more than 500 subjects each. One trial enrolled individuals receiving high-dose chemotherapy and the other enrolled individuals receiving radiation therapy for head and neck cancers. The chemotherapy trial failed to demonstrate any benefit over standard oral care. In the radiation therapy study, no differences were found; however, the iseganan group did have fewer cases of ulcerative oral mucositis and experienced less severe oral mucositis than the group that received standard care only (Giles et al., 2004; Trotti et al., 2004).

Not Recommended for Practice

Although early studies appeared to demonstrate some benefit of the use of **chlorhexidine** for chemotherapy-induced mucositis, this benefit has not been repeated in subsequent studies, nor has it been shown for radiation-induced mucositis (Scully et al., 2006). Review of other studies indicates chlorhexidine is not effective in reducing the severity of mucositis. It was believed that chlorhexidine could impact mucositis by significantly suppressing oral flora; however, that claim also is not shown in the research literature (Scully et al.; Shih et al., 2002). The MASCC (2005) guidelines indicate that chlorhexidine should not be used to treat established oral mucositis because its superiority to bland rinses has not been established and it may contain alcohol (Rubenstein et al., 2004). Other reports indicate rinse-induced discomfort, taste alteration, and teeth staining (Cheng et al., 2001, 2004; Dodd et al., 2000; Eilers, 2004; Pitten, Kiefer, Buth, Dowlken, & Kramer, 2003).

GM-CSF is a hematopoietic growth factor that promotes neutrophil development and regulates functions of mature leukocytes and macrophages in the dermis and submucosa (Shih et al., 2002). Although three smaller studies (N = 31, 68, and 61, respectively) have demonstrated moderate benefits with **GM-CSF mouthwashes** (Henja et al., 2001; Mantovani et al., 2003; Nicolatou-Galitis et al., 2001), all of them had substantial

methodologic flaws. One large (N = 90), well-controlled study failed to demonstrate a benefit (Dazzi et al., 2003), and another randomized control trial (N = 41) also demonstrated no benefit (Valcarcel et al., 2002). The updated MASCC (2005) guidelines indicate that GM-CSF mouthwashes should not be used for the prevention of oral mucositis in the transplantation setting (Rubenstein et al., 2004). That recommendation also is supported in systematic reviews that discuss this agent (Kwong, 2004; Shih et al.; von Bultzingslowen et al., 2006).

Sucralfate is a basic aluminum salt of sulphated sucrose that is used to treat gastric and duodenal ulcers. It is believed to protect the mucosa from local irritants. A number of smaller studies have produced conflicting results with this agent; however, double-blind studies have not demonstrated a benefit (Castagna et al., 2001; Dodd et al., 2003; Etiz et al., 2000; Nottage et al., 2003). Those studies used varying doses and frequencies, making comparison difficult. Sucralfate is not recommended because of the lack of tolerability related to nausea and other gastrointestinal effects, including rectal bleeding (Eilers, 2004; Kwong, 2004; MASCC, 2005; Rubenstein et al., 2004; Scully et al., 2006; Shih et al., 2002).

Expert Opinion

Bland Rinses

Rinses are used to remove loose debris and aid with oral hydration. Bland rinses include 0.9% saline (normal saline), sodium bicarbonate, and a saline and sodium bicarbonate mixture. Typical mixtures contain one teaspoon salt or sodium bicarbonate per pint of water. Any of those rinses can be administered at room temperature or refrigerated, and all are inexpensive. Patients should be instructed to take a tablespoon of the rinse, swish it in the oral cavity for at least 30 seconds, and expectorate. Sodium bicarbonate reduces the acidity of oral fluids, dilutes accumulating mucus, and discourages yeast colonization (Dodd et al., 2000; Eilers, 2004; Rubenstein et al., 2004; Scully et al., 2006; Shih et al., 2002).

Table 2. Assessment Tools and Grading Scales

TOOL OR SCALE	COMPONENTS ADDRESSED	RATING APPROACH	COMMENTS
National Cancer Institute Common Toxicity Criteria (NCI-CTC)	Clinician assessment: areas of anatomy not clearly indicated	0 = none; 1 = erythema of the mucosa; 2 = patchy ulcerations or pseudomembranes; 3 = confluent ulcerations or pseudomembranes, bleeding with minor trauma; and 4 = tissue necrosis, significant spontaneous bleeding, and life-threatening consequences	Does not include functional or subjective assessment or pain
Oral Assessment Guide (OAG)	Clinician assessment: voice, swallow, lips, tongue, saliva, mucous membranes, gingiva, and teeth and dentures	Each aspect is rated on a 1–3 scale: 1 = normal, 2 = altered but not loss of function or barrier breakdown, and 3 = loss of function or barrier breakdown	Clear, concise, and clinically relevant; does not differentiate areas of mucous membranes
Oral Mucositis Assessment Scale (OMAS)	Clinician assessment: erythema and ulceration in eight anatomic locations of the oral cavity Patient report: subjective outcomes such as pain, difficulty swallowing, and ability to eat	Erythema 0 (none) to 2 (severe); ulceration formation 0 (no lesion) to 3 (> 3 cm^2); patient report on 100 mm visual analog scales 0 (no problem) to 100 (worst problem); ability to eat categorical scale-types of food	Includes quantifiable function and objective and subjective measures, and focuses on mucous membranes; does not include other oral cavity changes, and may require more training than shorter tools
Oral Mucositis Index (OMI)	Clinician assessment: lips, labial mucosa, buccal mucosa, floor of mouth, soft palate, and tongue; all areas assessed for atrophy, ulcers, and/or erythema	Atrophy, ulceration, erythema, and edema; scored from 0 (none) to 3 (severe) and are summed for total score	Strong dental focus; does not include functional or subjective assessment of pain
Western Consortium for Cancer Nursing Research (WCCNR)	Clinician assessment of subjective variables: lesions, color, and bleeding	Rated on a 0–3 scale: 0 = no lesions, pink color, no bleeding; 1 = 1–4 lesions, slightly red color, no bleeding; 2 = > 4 lesions, moderate red color, bleeding occurs with eating and oral hygiene; 3 = lesions are coalescing, very red color, bleeding is spontaneous	Global scale that can reflect clinical status and outcomes; refined in 1998; based on elimination of five measures other than lesions, color, or bleeding; mixed objective, subjective, and functional variables; and difficult to score precisely
World Health Organization (WHO)	Clinician assessment: areas of anatomy not clearly indicated	0 = none; 1= soreness with or without erythema; 2 = erythema, ulcers, patient can swallow food; 3 = ulcers with extensive erythema, patient cannot swallow solid food; and 4 = alimentation is not possible	Swallowing and eating addressed; pain is not explicitly addressed.

Note. Based on information from Eilers et al., 1988; McGuire et al., 2002; National Cancer Institute, 2006; Western Consortium for Cancer Nursing Research, 1998; World Health Organization, 1979.

Implications for Nursing Practice and Research

Measurement is essential to the establishment of sound evidence-based care. A major impediment to the advancement of care related to the prevention and treatment of mucositis in cancer care has been related to assessment and measurement of mucositis (Eilers & Epstein, 2004). Studies to date have not consistently used valid and reliable instruments to document changes in the oral cavity. In addition, many clinical settings do not use a valid and reliable assessment tool in daily practice. Mucositis assessment and grading scales have been reviewed for use by clinicians (Eilers & Epstein; Sonis et al., 2004). Eilers and Epstein identified questions to guide the selection of an instrument for mucositis assessment including: What information regarding the oral cavity is needed? How will the collected data be used? Does the instrument address the necessary area of concern? Does the instrument have established validity and reliability? Is the instrument able to provide the specificity needed? Who will be conducting the assessment? What skill or training is needed to complete the assessment?

Tools to consider include the Oral Assessment Guide (Eilers, Berger, & Petersen, 1988), Oral Mucosa Rating Scale (Kolbinson, Schubert, Flournoy, & Truelove, 1988), Oral Mucositis Index (McGuire et al., 2002; Schubert, Williams, Lloid, Donaldson, & Chapko, 1992), and Oral Mucositis Assessment Scale (Sonis et al., 1999). Grading scales to consider include the Western Consortium for Cancer Nursing Research (1998) stomatitis staging system, World Health Organization (1979) Cancer Treatment Toxicity, and National Cancer Institute (2006) Common Toxicity Criteria. See Table 2 for a summary of those tools and scales.

Nursing has an excellent opportunity to impact patient outcomes through diligent attention to evidence-based oral care. An organized approach for determining past history and practices related to oral care and oral health in general, coupled with routine use of a valid and reliable instrument for the assessment of the oral cavity, is foundational to professional nursing care of patients receiving mucotoxic antineoplastic therapies. Although the optimum oral care program is best accomplished through a well-organized, multidisciplinary effort with dental professionals, physicians, and nurses (MASCC, 2005), nursing must be willing to lead the effort when other disciplines are not available or attentive to this area of cancer care.

Initiation
DNA and non-DNA damage, direct cellular injury to basal epithelial cells, and generation of reactive oxygen species

Primary Damage Response
Damage in genes is followed by upregulation of genes that results in the production of a range of destructive proteins and molecules such as the pro-inflammatory cytokines that lead to apoptosis and tissue injury.

Signal Amplification
Substances from the damage response phase provide a positive feedback loop that drives the destructive process forward.

Ulceration
The oral epithelium breaks down and ulcerates. Infections may occur at this stage as it frequently corresponds with neutropenia and an increase in gram-negative organisms.

Healing
Biologically dynamic phase with signaling from the submucosal extracellular matrix, stimulating the migration, differentiation, and proliferation of the healing epithelium

Figure 2. Sonis' Biological Phases of Mucositis
Note. Based on information from Scully et al., 2006.

Awareness of the proposed pathophysiologic model by Sonis et al. (2004) can serve to guide interventions and future efforts to improve outcomes. The stages of mucositis proposed in this model are explained in Figure 2 and may be beneficial to guide decisions regarding interventions. Although research to date has not been able to identify a universally effective intervention for the prevention or treatment of mucositis, an integrated standard approach to oral care should be used (Rubenstein et al., 2004). Establishment of such a standard can serve as the first step toward improved oral care practices. Education of staff, patients, and family members should be incorporated in this approach.

Although standard plans should provide the basis for care, nurses must strive to develop individualized plans that are designed to provide the best results for each patient. This includes evaluating patients' ability and willingness to perform the proposed oral care. Limited adherence to the best plan is less desirable than a compromise that addresses the patients' preferences and abilities and avoids harmful products. Groups of patients such as those receiving high-dose therapies and those receiving treatment for head and neck cancer are at increased risk for severe oral mucositis and complications; thus, they should receive focused attention.

Unfortunately, a mucotoxicity rating scale for cancer treatments that could serve to aid clinicians in the prioritization of patients most likely to benefit from interventions is not yet available. Documentation of oral cavity changes based on assessment using a valid and reliable instrument will aid in the advancement of knowledge about mucotoxicity of various antineoplastic therapy protocols. Patients receiving less toxic regimens may not experience mucositis and so may not require the more intensive, often expensive, interventions.

Summary

Ongoing research related to preventing and treating oral mucositis shows some promising directions, including new growth factors, and novel therapies, such as LLLT. Further study is needed to determine the role for those therapies. At this time, oral care, cryotherapy, and palifermin are the only management strategies for which sufficient evidence for practice exists. Additional study is required to determine the frequency of the elements in an oral care protocol and the use of palifermin with additional populations. Oncology nurses are crucial to developing the evidence in those areas. Nurses must ensure that the assessment tools used are valid and reliable. Consistency of assessment in this area allows for better comparison of interventions. As new interventions become available, nurses will continue to directly impact patient outcomes. Evidence-based practice tools, such as the PEP cards,

will allow nurses to access current information more easily and employ the appropriate interventions for specific patient needs.

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Appendix. Putting Evidence Into Practice® Card on Mucositis

What interventions are effective for managing oral mucositis in people receiving treatment for cancer?

RECOMMENDED FOR PRACTICE

Interventions for which effectiveness has been demonstrated by strong evidence from rigorously designed studies, meta-analyses, or systematic reviews and for which expectation of harms is small compared with the benefits

Oral Care Protocols

Oral care protocols developed by multidisciplinary teams may reduce the severity of oral mucositis. These protocols should include educational components for patients and staff.[1-3] Oral assessment with a validated tool should be used regularly to assess function, pain, and the oral cavity. The inclusion of dental professionals is recommended throughout treatment and follow-up.[2]

Basic oral care should include using a soft toothbrush that is replaced regularly.[2,3] See the Expert Opinion section for other important aspects of oral care.

LIKELY TO BE EFFECTIVE

Interventions for which there is evidence from a single rigorously conducted controlled trial, consistent evidence from well-designed controlled trials using small samples or from meta-analyses/systematic reviews using small samples, or evidence from guidelines developed from evidence and supported by expert opinion

Cryotherapy for Patients Receiving Bolus Chemotherapy With Short Half-Life (Bolus 5-Fluorouracil, Melphalan)

Cryotherapy has a significant effect on the reduction of oral mucositis in patients receiving rapid infusions of either 5-fluorouracil or melphalan (L-PAM).[4-8] The effectiveness is based on vasoconstriction of the circulation in the oral cavity and the short half-life of these agents. Cryotherapy has not yet proved to be beneficial with other agents.[9-11]

The optimum duration of cryotherapy requires further systematic investigation, as studies to date have been inconsistent. Based on current knowledge, patients should hold ice or ice-cold water in their mouth for five minutes prior to the infusion, during the infusion, and for 30 minutes after completion of the infusion. Compliance with the cooling has been varied and presents concerns for individuals who do not tolerate coldness in their oral cavity. It is not indicated in patients who are receiving capecitabine or oxaliplatin because of problems with exposure to coldness.[9,10-12]

Palifermin for Patients Undergoing Autologous Hematopoietic Stem Cell Transplant (HSCT) for Hematologic Malignancies

Palifermin is a recombinant human keratinocyte growth factor that stimulates growth of epithelial cells. This drug has been shown to reduce severity and duration of oral mucositis in patients with hematologic malignancies receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplant.[13] Palifermin is given at a dose of 60 mcg/kg/day IV for three days prior to the beginning of the conditioning regimen and for three days post-transplant for the prevention of oral mucositis. Because of the high cost of this agent, it should be used for those patients most likely to develop severe mucositis. The most common side effects include mild rash and taste changes.[2,11,13,14]

For information on investigational drugs used in managing oral mucositis, see the detailed ONS PEP card at www.ons.org/outcomes.

EFFECTIVENESS NOT ESTABLISHED

Interventions for which there are currently insufficient or conflicting data or data of inadequate quality

Allopurinol

Although initial small trials of allopurinol mouthwashes found some positive treatment findings for oral mucositis, these results were not confirmed in controlled trials.[9,11,15]

Amifostine

The role of amifostine in the management of oral mucositis has not been established. It is currently recommended to reduce esophagitis induced by concurrent chemotherapy and radiation in patients with non-small cell lung cancer and for prevention of radiation proctitis in patients receiving standard-dose radiation for rectal cancer.[1,16] Further studies are needed to establish the use of amifostine for the management of oral mucositis.

Anti-Inflammatory Rinses

Anti-inflammatory rinses (Kamillosan Liquidum® [Asta Pharma AG], hydrocortisone, prostaglandin E1, and oral corticosteroids) have been examined in small studies, none of which produced significant results. Poor study design and inadequate sample sizes prevent definitive conclusions regarding these agents.[17]

Antimicrobial Agents

A wide variety of antimicrobial agents including polymyxin, tobramycin, amphotericin B, fluconazole, protegrin, and many others have been studied in a variety of doses and combinations.[17] No clear pattern of benefit has emerged, and little evidence exists to recommend the use of these agents.[18] One large placebo-controlled randomized trial has shown narrow-spectrum antibacterial lozenges to be effective in the setting of radiation.[11]

Benzydamine HCl

Benzydamine is used in Europe and Canada but has not been approved by the U.S. Food and Drug Administration for use in the United States. Benzydamine has been shown to produce a significant reduction in oral mucositis compared with placebo in patients receiving 0–5,000 cGy of radiation for head and neck cancer. This effect was not seen in patients receiving high single-day doses of radiation therapy ≥ 22 cGy/day. Patients rinse with 15 ml benzydamine for two minutes four to eight times daily before and during radiation therapy and for two weeks after completion of radiation therapy.[19]

Flurbiprofen Tooth Patch

Flurbiprofen is an inhibitor of COX-2, which is thought to contribute to the development of oral mucositis. Flurbiprofen also has antiproliferative activity. One trial (N = 22) found a slight delay in the development of mucositis but no effect for prevention. Pain scores were higher in the flurbiprofen group. Study size and administration may have been too small to see effects.[20]

Granulocyte–Colony-Stimulating Factor (G-CSF) (Subcutaneous)

Studies of G-CSF demonstrate conflicting results. Two randomized studies showed a reduction in oral mucositis incidence,[21,22] whereas several other studies have not demonstrated any effects.[11]

Granulocyte Macrophage–Colony-Stimulating Factor (GM-CSF) (Subcutaneous)

Evidence is conflicting for GM-CSF for the treatment of oral mucositis. GM-CSF may or may not effectively treat mucositis. Study sample sizes were small, and patient dropout rate was high because of intolerable side effects.[11,14,17,23,24]

Immunoglobulin

Studies using intramuscular injections of immunoglobulin have shown a reduction in oral mucositis; however, these studies are small (N = 22), and no studies have had published data since 1997.[9,17]

L-Alanyl-L-Glutamine

The effectiveness of glutamine in treating oral mucositis has not been established. One small study (N = 29) demonstrated a moderate effect over mucositis intensity ($p = 0.044$).[25] All patients in this study were given supplemental oral nutrition. Glutamine has not been shown to prevent mucositis.[25]

Low-Level Laser Therapy (LLLT)

Seven small studies using LLLT have been conducted to date, demonstrating lack of toxicity and evidence of potential benefit for prevention, treatment, and pain control related to oral mucositis.[1,10,11,26,27] Laser therapy requires specialized equipment and training, which is not widely available. One study suggested using LLLT where available to reduce the incidence of oral mucositis and the associated pain in patients receiving chemotherapy or chemoradiation before HSCT.[1]

Multiagent ("Magic" or "Miracle") Rinses

Multiagent rinses typically include lidocaine, Benadryl® (McNeil PPC), and Maalox® (Novartis Consumer Health) or other similar agents. Some patients commented that the mouthwash made their mouth "numb," which is a concern because of potential injury. Additionally, some formulations of these agents may contain alcohol, which should be avoided. Little evidence exists to demonstrate the effectiveness of these rinses.[28,29]

Oral Aloe Vera

Only one small study (N = 58) of aloe vera was identified.[30] Although patients in the aloe vera arm had a lower maximal oral mucositis severity grade, this was not statistically significant. No other findings were statistically significant.

Pilocarpine

Early trials indicated that pilocarpine has some benefit in reducing the severity of oral mucositis; however, this was not demonstrated in a recent controlled trial. Side effects of this agent include tachycardia and palpitations.[31,32]

Povidone-Iodine (Oral)

Although earlier trials demonstrated significant reductions in onset, incidence, total duration, and worst grade of oral mucositis with oral povidone-iodine,[9,17,29] a more recent randomized controlled trial (N = 132) did not.[33] Additionally, povidone-iodine was found to be less tolerable than normal saline. This agent is not to be used in patients with new granulation tissue, as it inhibits cell growth. Swallowing povidone-iodine is absolutely contraindicated.

Tetracaine

One uncontrolled study (N = 50) demonstrated a reduction in oral cavity pain and fewer radiation treatment interruptions when patients were treated with tetracaine gel applied approximately six times per day.[34]

Zinc Supplementation

One small randomized controlled trial (N = 30) determined that no grade 4 oral mucositis developed in the zinc group and that mucositis development was delayed in this group ($p < 0.01$).[35] Six weeks after the completion of radiation treatment, only one patient in the zinc group continued to have mucositis, whereas 10 of the 12 patients in the placebo group did. In a second trial (N = 97), similar results were found.[36] Optimal dose has yet to be determined.[35,36]

EFFECTIVENESS UNLIKELY

Interventions for which the lack of effectiveness is supported by evidence from a single rigorously designed controlled trial or consistent evidence from controlled trials using small samples or where meta-analyses/systematic reviews using small samples or guidelines developed by consensus/expert opinion indicate a lack of effectiveness

Iseganan

Iseganan failed to show adequate effect for oral mucositis related to high doses of chemotherapy or radiation therapy for head and neck malignancy in two multisite randomized controlled trials of more than 500 subjects each.[37,38]

NOT RECOMMENDED FOR PRACTICE

Interventions for which lack of effectiveness or harmfulness has been demonstrated by strong evidence from rigorously conducted studies, meta-analyses, or systematic reviews or interventions for which the costs, burdens, or harms associated with the intervention exceed anticipated benefit

Chlorhexidine

Chlorhexidine is not effective in reducing the severity of oral mucositis nor does it have significant effects on suppression or any type of oral flora.[17] The Multinational Association of Supportive Care in Cancer (MASCC) guidelines indicate that chlorhexidine should not be used to treat established oral mucositis because its superiority to bland rinses has not been established and it may contain alcohol.[1] Other reports indicate rinse-induced discomfort, taste alteration, and teeth staining.[28,29,39-41]

GM-CSF Mouthwash

GM-CSF mouthwash has not demonstrated any benefit in treating oral mucositis. The updated MASCC guidelines indicate that GM-CSF mouthwashes should not be used for the prevention of oral mucositis in the transplant setting.[1,2] This recommendation also is supported in systematic reviews that discuss this agent.[9,14,17]

Sucralfate

Sucralfate has not demonstrated any benefit in treating oral mucositis and is not recommended for practice because of a lack of tolerability related to nausea and other gastrointestinal effects, including rectal bleeding.[1,2,9,11,17,29,42-45]

EXPERT OPINION

Low-risk interventions that are (1) consistent with sound clinical practice, (2) suggested by an expert in a peer-reviewed publication (journal or book chapter), and (3) for which limited evidence exists. An expert is an individual who has authored articles published in a peer-reviewed journal in the domain of interest.

Oral Care Protocol

Although randomized controlled trials are lacking, experts agree that routine basic oral care is an important element of care for prevention and management of oral mucositis.[1,9,29] In fact, it would be regarded as unethical to withhold basic oral care as one arm of a research study in order to validate the benefit of such care. An oral care protocol consisting of at least the following elements should be included for all patients receiving treatment that places them at risk to develop oral mucositis.

Clinicians[1,17,28,29]

- Collaborate with a multidisciplinary team in all phases of treatment.
- Conduct a systematic oral assessment at least daily or at each patient visit. In the outpatient setting, teach patients to perform oral assessment daily. Teach patients when to report assessment findings to the clinician.
- Provide written instruction and education to patients regarding oral care. Verify understanding with return explanation and demonstration.

Instructions for Patients[1,2,9,11,17,28,29,39,40,43]

- Brush all tooth surfaces for at least 90 seconds at least twice daily using a soft toothbrush. Allow toothbrush to air dry before storing.
- Floss at least once daily or as advised by the clinician.
- Rinse mouth four times a day with a bland rinse (see the following section).
- Avoid tobacco, alcohol, and irritating foods (e.g., acidic, hot, rough, spicy).
- Use water-based moisturizers to protect lips.
- Maintain adequate hydration.

Bland Rinses

Rinses are used to remove loose debris and aid with oral hydration. Bland rinses include 0.9% saline (normal saline), sodium bicarbonate, and a saline and sodium bicarbonate mixture. Any of these rinses can be administered at room temperature or refrigerated, and all are inexpensive. Patients should be instructed to take a tablespoon of the rinse, swish it in the oral cavity for at least 30 seconds, and expectorate. Sodium bicarbonate reduces the acidity of oral fluids, dilutes accumulating mucus, and discourages yeast colonization.[1,11,17,28,29]

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Definitions of the interventions and full citations: www.ons.org/outcomes
Literature search completed through September 2006.

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