Nursing Interventions and Supportive Care for the Prevention and Treatment of Oral Mucositis Associated With Cancer Treatment

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Purpose/Objectives: To review novel approaches to assessing and managing patients with cancer who are at risk for oral mucositis.

Data Sources: Published research and review articles, books, conference presentations, and abstracts.

Data Synthesis: Oral mucositis is a major source of clinical morbidity among patients with cancer undergoing treatment, yet definitive management strategies continue to elude practitioners. A growing body of evidence suggests that a multifaceted, innovative, targeted approach to oral care provides an important foundation with which to reduce treatment-related morbidity.

Conclusions: Ongoing assessment and monitoring are critical to the effective management of oral mucositis. Targeted interventions that incorporate the basic principles of wound care with current knowledge about the temporal aspects of clinical manifestations, evidence-based standardized approaches to assessment, and utilization of novel therapeutics provide an important means by which to improve patient outcomes.

Implications for Nursing: Oral care protocols are essential components of oral mucositis management. Incorporating current knowledge of pathophysiology with a targeted, standardized approach may help to reduce overall morbidity and improve quality of life.

Key Points . . .

➤ Although oral mucositis remains a major source of clinical morbidity and reductions in quality of life among patients with cancer, a definitive approach for prevention or treatment continues to elude clinicians.

➤ Oral care protocols are essential components of an oral mucositis management program. To be effective, they must be evidence-based, goal-driven, and systematically and consistently applied.

➤ Ongoing assessment and monitoring are critical to effective oral mucositis management. A novel approach to identifying patients at highest risk and targeting interventions incorporates symptom cluster evaluation coupled with a thorough understanding of the principles of wound care and the temporal aspect of oral complications and their manifestations.

➤ Although progress in finding efficacious management strategies has been hampered by an insufficient evidence base, several promising new agents with multiple actions that provide safe symptom relief are in the research pipeline.

Mucositis, an inflammation that may or may not include ulcerations of the mucous membranes, affects an estimated 40%–100% of patients undergoing stomatotoxic chemotherapy, radiation therapy, and blood and marrow stem cell transplant (BMSCT) (National Cancer Institute [NCI], 2003). It remains a serious side effect of cancer treatment with implications for nursing. Mucositis is not confined to the oropharyngeal cavity and can affect the entire gastrointestinal tract. Oral mucositis, which results in disruption in the function and integrity of the oral cavity, can produce significant clinical morbidity (including pain, malnutrition, and local and systemic infections), cause treatment delays and dosage adjustments, increase hospitalizations and costs, and significantly affect functional status and quality of life (QOL). In fact, patients who experienced secondary oral complications associated with chemotherapy-induced oral mucositis reported significant declines in QOL that caused them to discontinue treatment (Redding & Haveman, 1999). Treatment delays, decreases in doses, and lack of adherence to treatments influence the effectiveness of cancer treatment delivered and, ultimately, the likelihood of optimum outcomes.

Unfortunately, definitive approaches to prevent and treat oral mucositis do not exist at the present time. Clinical interventions often are variable and lack standardization because data on the efficacy of one treatment versus another often are inconsistent or inconclusive. Additionally, patients are not educated routinely on how or why to care for their mouths or assessed for signs and symptoms of oral mucositis.

Despite these challenges, recent work that suggests a multifactorial pathophysiologic basis for mucositis, along with advances in approaches to assessment and the development of novel therapies, may facilitate targeted management strategies.

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Nurses are in a unique position to interact with patients with cancer prior to the initiation of therapy (Sadler et al., 2003) and throughout the course of treatment. Such interaction provides a strategic opportunity for oncology nurses to advocate for innovative, evidence-based approaches to oral care that will promote a decline in treatment-related morbidity.

The Variable Consequences and Challenges of Oral Mucositis

Mucositis results from a complex, sequential interaction of biologic events that occur simultaneously in multiple cells and tissues involving various elements (e.g., tissue factors, cytokines) at all levels (Sonis, 2003). Once initiated, a cascade of events involving proinflammatory cytokines, macrophages, and local tissue factors results in alterations in the mucosal environment, clinically apparent ulcerations and lesions, and amplification of tissue injury, followed by a general period of healing (Sonis). This process, which is described in greater detail by Dodd (see pp. 5–11), involves different phases, which supports the idea that mucositis is a process and not a single event (Eilers, 2001). This idea is particularly critical for management strategies, in that it implies that mucositis varies in both appearance and manifestations, depending on the specific time point in the biologic process and the location of tissue changes.

Importantly, mucositis does not affect every patient with cancer, and not all cancer treatments cause mucosal changes. Some treatments may cause varying degrees of mucositis. Additionally, not only does mucositis manifest itself in various ways (e.g., mouth ulcerations, severe throat pain, gastrointestinal discomfort), but its resolution may vary depending on individual patient characteristics and the nature of treatment. For example, some clinicians may assume that healed ulcerations and resumption of swallowing are signs that oral mucositis has resolved completely, but long-term changes often exist in the oral cavity. Not only can numerous changes that occur at the epithelial molecular and cellular levels persist (Sonis, 2003), but longer-term problems, such as altered taste or xerostomia, may occur in certain patients (e.g., those receiving radiation therapy). These variable experiences are complicated further by the tendency of many patients to minimize their degree of discomfort as a method of coping, even though research has shown that, when asked directly, patients describe "distinct periods of misery" (Borbasi et al., 2002).

Oral Mucositis and Quality of Life

Although oral mucositis often is included among the symptoms accompanying cancer treatment that have the potential to alter QOL, the vast majority of research has focused on the physical manifestations of oral mucositis (Dodd, Dibble, et al., 2001). Little doubt exists that mucositis has the potential to cause significant problems that alter morbidity. However, when a small panel of patients and practitioners were convened to identify the most important consequences of oral mucositis, diminished QOL and functional status were included among the top four (following oral pain, the need for opioid analgesics, and inability to eat soft foods) (Bellm et al., 2002).

Although patients often are prepared for the physical aspects of oral mucositis, rarely are they aware of the potential psychological sequelae, such as the inability to enjoy the social pleasures that accompany eating and drinking (Borbasi et al., 2002). Fortunately, for many patients, the psychological aspects of oral mucositis are time limited. If the physical symptoms that accompany mucositis persist for a longer period of time, or if mucosal damage causes permanent changes in saliva or swallowing, they may influence QOL, even though the mucositis itself usually resolves. Conversely, although the breakdown of the mucosal barrier allows life-threatening infections to enter the bloodstream, prevention or adequate treatment will facilitate resolution and limit their impact on QOL.

This point recently was demonstrated in a longitudinal study that compared QOL and affective state of patients receiving chemotherapy who developed oral mucositis to those who did not (Dodd, Dibble, et al., 2001). Seventy-seven patients completed the Multidimensional Quality of Life Scale, Cancer version (MQOLS–CA) and the Profile of Mood States (POMS) at the start of therapy (time 1) and again if they developed oral mucositis during their three cycles (monthly) or if they did not and were exiting the study (time 2). MQOLS–CA is a 33-item scale that measures five dimensions of QOL, with higher scores reflecting better QOL, and POMS is a 37-item scale that measures affective or mood states. Over time, MQOLS–CA scores decreased significantly and total POMS scores increased significantly for the entire sample, meaning that all patients in the study, regardless of whether they developed oral mucositis, experienced a decline in QOL and an increase in mood disturbance. However, patients who developed oral mucositis anytime during treatment (n = 28) had twice the increase in total mood disturbance than patients who did not (p = 0.03). Both the depression and anger subscale scores on the POMS significantly increased over time for the entire sample (p < 0.001) but again doubled in patients who developed oral mucositis (Dodd, Dibble, et al.). Because the majority of research on chemotherapy-induced mucositis has been focused on the physical aspects of this side effect, studies evaluating its impact on mood and QOL are especially informative and emphasize the need for effective intervention strategies.

The Basic Principles of an Oral Care Protocol: Building a Framework for Nursing Interventions

Oral care protocols are essential components of an oral mucositis management program. Data suggest that when systematically applied, self-care protocols have the potential to significantly decrease the incidence, severity, and duration of oral sequelae (Sadler et al., 2003). Moreover, when patients are provided with the proper tools (i.e., didactic information that includes the basic principles of good oral hygiene, skill enhancement, and supportive follow-up) (Larson et al., 1998), they are more inclined to assume responsibility for self-care. Yet, despite its acknowledged importance, oral care often is one of the first things to be set aside when nursing workloads are excessive (McGuire, 2003). In fact, standards of oral care are used inconsistently in patients undergoing cancer therapy and are nonexistent in many institutions (McGuire; Mueller, Millheim, Farrington, Brusko, & Wiser, 1995). Common barriers to instituting such standards are listed in Table 1. To improve the assessment and management of oral mucositis, each of the barriers listed in the table must be addressed.

Table 1. Common Barriers to the Implementation of Oral Care Standards

Barrier	Associated Factors
Knowledge gaps	Rationale for care, identification of at-risk patients, assessment tools, oral sequelae, effective interventions, outdated information, and lack of education
Reliance or overreliance on tradition	Anecdotal practices
Inconsistent or absent oral assessment	Absent evaluations, failure to use tools consistently, use of multiple tools in the same institution, inadequate assessment and documentation, and inconsistent use of data to guide practice
Diverse regimens and practices	Use of a wide variety of agents, regimens, equipment, and practices
Insufficient or conflicting evidence base	Lack of studies, conflicting results in well-executed studies, inconsistent methodology, and selection of oral care regimens based on flawed research
No gold standard	Lack of universal agreement as to what constitutes ideal universal oral care, including assessment, prophylactic and therapeutic agents, oral care protocols, and relevant clinical outcomes
Administrative and clinical issues	Low staffing, excessive workloads, reliance on tradition, and lack of support for staff education
Lack of multidisciplinary collaboration	Organizational structure, parallel activities, disciplinary isolation, and dentists often being excluded

Note. Based on information from McGuire, 2003.

Information and Decision Making: Identifying High-Risk Patients

Although basic oral care is important for all patients with cancer, time and work constraints limit the ability to focus on thorough oral care for all patients on a regular basis. Therefore, identifying patients at highest risk for the development of oral care problems is important so that their needs can be addressed in a timely manner. Targeting high-risk patients for interventions is not done at the expense of patients at lower risk who develop oral mucositis. Rather, risk identification can be used as a guide for determining the frequency of follow-up visits and scheduled nursing assessments during the peri- and post-treatment periods.

High-risk patients include those who receive antineoplastic agents that interfere with DNA synthesis and have a direct effect on the epithelium (e.g., 5-fluorouracil, bulsulfan, cyclophosphamide, methotrexate), as well as the very young or very old. Patients with periodontal disease or poor oral health also are at high risk for developing oral mucositis. Individuals with hematologic malignancies tend to have more mucositis than those with solid tumors (Eilers, 2001). Additionally, kidney disease and poor renal status during chemotherapy have been identified as contributing to severe oral mucositis (see Table 2).

Evidence and Standards of Care

Practice should be evidence-based whenever possible. This approach entails a thorough examination of oral care practices and institutional guidelines, followed by an assessment of published literature and how data might be applicable to specific patient populations in the clinical setting. Although cumbersome, available studies and articles should be delineated by topic (e.g., assessment, prevention, treatment) and examined for the strength of the evidence (e.g., Was the trial randomized and controlled?, Does an expert consensus exist?), as well as for quality and consistency (Stricker & Sullivan, 2003). Ultimately, melding evidence-based practice with current nursing and institutional practice relies on multidisciplinary collaboration. This approach can help to ensure that clinical practices will be standardized and adopted for widespread use.

Goals and the Oral Care Protocol

Optimally, oral care should focus on achievable outcomes (e.g., prevention, alleviation of symptoms, promotion of healing)

Table 2. Patient-Specific Risk Factors Potentially Related to the Development of Oral Mucositis

Risk Factor	Potential Mechanism
Age	Young children: • Number of mitoses in the basal epithelium makes cells more sensitive to toxicities. • Higher rate of hematologic malignancies producing prolonged and intensive myelosuppression Older individuals: • Physiologic declines in renal function • Decreased healing rates
Periodontal disease and oral health	Xerostomia prior to treatment may impair permeability of the oral mucosa, reduce oral pH (from a normal 7.0 to ≤ 5.5), and cause tooth decay and gingivitis. Increased debris contributes to infection rates.
Nutritional status	High sugar intake or protein and calorie malnutrition may increase dental decay and contribute to dehydration that irritates and delays oral mucosal healing.
Medications (e.g., opioids, antidepressants, phenothiazines, antihypertensives, antihistamines, diuretics, sedatives)	May cause xerostomia, which promotes periodontal disease and predisposes oral cavity to bacterial and fungal overgrowth
Tobacco and alcohol use and abuse	Exacerbates periodontal disease and irritates oral mucosa
Immune dysfunction and neutrophil count	Neutrophil levels < 3,000–4,000 cells/mm³ associated with 5-fluorouracil and other infusions. Weekly treatment may significantly increase risk.
Oxygen therapy	Oxygen dries mucosal lining, which is especially problematic in acute care patients.
Changes in breathing	Examples include tachypnea and mouth breathing, which dry mucosal lining and are especially problematic in acute care patients.

Note. Based on information from Beck, 1999.

and on the time point in the biologic process when the patient is being treated. An oral care protocol can be enhanced by thinking about the mucosal changes in the oral cavity in the same manner that care of other wounds is planned.

- If debris is present, it should be removed or cleaned.
- If excessive drainage or moisture exists, the goal is to decrease it.
- If the area is dry, providing moisture becomes the focus.
- If the area has new granulation tissue or is healing, steps should be taken to avoid traumatizing developing cells.

For example, if ulcerative lesions are present in the mouth, the initial goal becomes pain control through the use of topical and systemic analgesics. Prevention of infections that can enter the bloodstream through open portals also is critical. However, patients with severe ulceration may be reluctant to perform oral care if the pain is not controlled adequately. Removal of accumulated debris that can serve as a medium for infection is fundamental. Treatment of infections that are present should be targeted to specific organisms. Because patients likely will develop yeast infections, prophylaxis should be considered. Prophylaxis also is warranted when patients have an elevated herpes simplex virus titer.

Nursing Assessment and Interventions

Self-Care

At present, available oral care strategies have a strong potential to decrease problems associated with mucositis but may not prevent them altogether. Still, steps to instill the importance of routine self-care are imperative to an overall treatment strategy if morbidity is to be reduced. Regardless of patient and treatment specifics, a basic oral care protocol for patients who undergo cancer therapy should incorporate the principles of good oral hygiene (Larson et al., 1998), including when and how to care for the mouth (see Figure 1). During the pre- and peritreatment periods, the focus is on promotion of good oral hygiene to reduce the likelihood of oral cavity problems. An oral care protocol, which ideally starts about two weeks before therapy is initiated, should include detailed information about toothbrush types (e.g., soft bristle, foam, or sponge that easily fits into a patient's mouth and facilitates reaching all areas easily); when brushes should be replaced; the need for consistent, regular, and thorough brushing; daily flossing; and rinsing with water twice daily (Larson et al.). If possible, nurses should instruct patients to have small bottles of water on hand for rinsing (unused portions should be discarded daily) and a timer to ensure that teeth are brushed for a full 90 seconds (Larson et al.). Instructions for denture wearers are slightly different (see Figure 1) and include denture removal every time oral care is performed, regular cleansing, and cessation of use except for eating when mucous membrane breakdown occurs.

Using an oral assessment instrument (e.g., Eilers' Oral Assessment Guide [OAG]), patients and family members should be instructed on how to examine the oral cavity, how to differentiate between what is normal and what is not, and when to notify a nurse of any changes (Larson et al., 1998) (see Figure 2). Distribution of essential tools, including dental mirrors, penlights, dental floss, and proper toothbrushes, may facilitate oral care and daily assessment of the oral cavity.

A key aspect of the PRO-SELF® Mouth Aware program (which was instituted as part of a series of randomized, con-

Oral hygiene instructions for patients and family caregivers
- Brush all tooth surfaces, including the inner, outer, and chewing surfaces, gently for at least 90 seconds at least twice daily (after breakfast and before bedtime).
- Tips for proper brushing
  - Make sure that bristles are soft and fit into your mouth comfortably.
  - Place toothbrush at a 45-degree angle against gums.
  - Move back and forth gently using short strokes.
  - Brush tongue to remove bacteria and freshen breath.
- Use a foam toothbrush or swab as advised by your clinician when regular brushing is too painful.
- Floss at least once daily.
- Tips for optimal flossing
  - Break off about an 18-inch strip of floss and wind it around both middle fingers.
  - Use your thumbs and forefingers for leverage to guide the floss between teeth with a gentle motion into the space between the tooth and gum.
  - Gently rub the floss against the tooth and away from the gum in an up and down motion.
  - Never snap the floss out of the tooth.
- Rinse afterward with water or a bland rinse for at least 30 seconds.
- If you wear dentures
  - Remove them every time you perform oral care.
  - Soak dentures daily in an antimicrobial solution and clean water.
  - Avoid wearing ill-fitting dentures before, during, and right after your treatment.
- Avoid tobacco, alcohol, and rough, course, salty, too hot, spicy, or acidic foods before, during, and after treatment.
- Dietary tips
  - Cook food until it is tender.
  - Cut food into small pieces.
  - Use gravies and sauces to moisten food.
  - Ingest a lot of liquids.
  - Eat protein-based softer foods, such as cottage cheese and scrambled eggs.
  - Include puddings, custards, and gelatins in the diet.
  - Ingest sherbets, gelatin, and other frozen desserts in moderation.
  - Eat soft, low-acid fruits, such as watermelon, bananas, and cantaloupe.
- If you have frequent dry mouth or decreased saliva, suck on nonirritating, sugar-free drops or chewing gum or sip water as instructed by your clinician.
- Use water-based moisturizers to protect lips against trauma.
- Use oral rinses, topical coating agents, and topical anesthetics as directed by your clinician.
- Call your clinician if you experience any bleeding, discomfort, irritation, or pain.

Figure 1. Systematic Basic Oral Care for Patients With Cancer

Note. Based on information from Beck, 1999; National Institutes of Dental and Craniofacial Research, 2002; Wilkes, 1998; Yeager et al., 2000.

trolled oral mucositis trials and upon which these recommendations are based) was skill building and education among the nurses who participated. All nurse participants received direction on the program's purpose and were provided with specific information about the tools patients need to self-administer oral care (Larson et al., 1998). Importantly, an emphasis was placed on the nurses' personal style of patient interaction, which served as the basis for supportive care. This approach was based on the belief that once nurse-patient relationships are established, patients are more receptive to encouragement and problem solving (Larson et al.). The program also provided nurses with an opportunity to assess and expand patients' self-care abilities on an as-needed basis. Importantly, nurse-patient interaction begins

During and after treatment

At least once daily, use a flashlight and mirror to carefully examine the mouth, including the lips, gums, and tongue, for sores, ulcers and lesions, pimples, red areas, white patches, or spots.

Call the nursing staff at your treatment center if you observe or experience any of the following conditions.

- Sores
- Ulcers and lesions
- Pimples
- Red areas
- White patches
- Pain in the mouth
- Extremely dry mouth
- Difficulty eating, chewing, or swallowing
- An unusual amount of bleeding

Figure 2. Patient Self-Assessment

the moment a patient is introduced to an oral care protocol and continues throughout the time that he or she uses it.

Assessment

Adequate management of oral cavity changes relies on on-going assessment and monitoring (Eilers, 2001). Assessment and monitoring should be initiated at about the same time that patients are being introduced to the concept of self-care. Establishing a baseline during this time can facilitate the ability to track changes throughout the treatment period so that interventions can be modified accordingly and provide an opportunity to reinforce the importance of self-care among patients and their families or caregivers.

Ideally, assessment should include thorough examination of the oral cavity, including lips, tongue, gingivae, and other surfaces; palpation of visible lesions; and evaluation of function (e.g., swallowing, talking). Ensuring appropriate lighting and oral cavity exposure will enhance visual assessment. Interaction with patients will provide essential information regarding function. Key observable alterations in the oral mucosa that should raise red flags for present or future complications include color changes, moisture changes, cleanliness issues, changes in mucosal integrity, and edema of the lips or tongue (Beck, 1999) (see Figure 3).

Early in the assessment process, efforts should be made to identify, treat, and eliminate sources of oral trauma and irritation, including low-grade and acute infections, tissue injury, dental decay, periodontal disease, endodontic disease, mucosal lesions, and trauma; remove ill-fitting dentures; and ar-

- Color changes, including pallor, erythema, white patches, discolored lesions, and ulcers
- Moisture changes reflecting salivary impairment, including increased or decreased amounts and changes in quality or tenacity of secretions
- Cleanliness issues, including debris, coating, bad odor, and tooth discoloration
- Changes in mucosal integrity, including cracks, fissures, ulcers, blisters, and lesions that are isolated, clustered, patchy, confluent, or generalized
- Edema of the lips or tongue

Figure 3. Observable Alterations in the Healthy Oral Mucosa That May Influence Later Treatment Complications

Note. Based on information from Beck, 1999.

range for extraction of problematic teeth. Despite their crucial contribution to preventing dental disease and related oral complications during and after cancer treatment, dentists and hygienists often are excluded from multidisciplinary oral cancer care efforts (McGuire, 2003). Preexisting dental disease constitutes a reservoir of pathogenic and opportunistic infections that also contribute to local infections (Dodd et al., 2003) and requires careful management by knowledgable professionals.

Increasingly, nurses are incorporating the use of solid and reliable instruments to assess changes in the oral mucosa during cancer treatment. Selection of tools should be goal driven, in that the principles of wound care also can be used to guide selection of appropriate tools. For example, specific oral cavity changes evident during oral examination, such as saliva function, might warrant selection of the OAG (which was developed for direct care practitioners and is readily adaptable for use by nurses and patients) because this tool provides an assessment of overall changes in the oral cavity rather than just a measure of mucositis alone. A detailed discussion of the OAG and other instruments is on pp. 5–11). An awareness of potential oral complications associated with cancer therapies (see Table 3) also facilitates the assessment process, not only in terms of selection of assessment tools based on treatment goals but also the more temporal aspects. For example, patients with severe infections, those who require oxygen therapy, and individuals who breathe through their mouths might benefit from more frequent assessments (Miller & Kearney, 2001).

The Importance of Symptom Clusters

Just as the use of the concept of "symptom clusters" is meaningful in addressing care of cancer treatment-related effects in general, it also has relevance in terms of oral cavity changes. A symptom cluster is defined as three or more concurrent symptoms that are related to one another but are not necessarily of the same etiology (Dodd, Miaskowski, & Paul, 2001). Researchers have proposed that the presence of concurrent symptoms may act synergistically to predict future morbidity (Dodd, Miaskowski, et al.). In oral mucositis, symptoms that cluster together include ulcerative lesions, bleeding, and pain. In turn, pain interferes with eating and speech. These symptoms have been significantly correlated with OAG scores. Xerostomia and hemorrhage are two other oral cavity changes that do not occur in isolation but rather cluster with other changes in the oral cavity. Nursing interventions should start with assessment to identify the cluster of symptoms that are present and then propose oral care to address the problems identified.

Current Treatment Strategies

Although interest in prevention and treatment of mucositis is widespread, limited progress has been made in finding an efficacious management strategy (Eilers, 2001), and oral complications remain a major source of morbidity despite the availability of a wide variety of agents. An important rationale for the diversity of regimens used across institutions and even in individual institutions has been the lack of a sufficient evidence base with which to make informed treatment decisions (McGuire, 2003). Not only do few well-designed or well-executed studies exist, but those that do meet higher standards often fail to demonstrate consistent findings (McGuire). Additionally, reporting

Table 3. Oral Complications Associated With Cancer Therapy

Regimen	Common Oral Complications	Comments
Chemotherapy	Oral mucositis Acute oral pain Xerostomia Infections of mucosa, dentition or periapices, and periodontium Disruption of food and fluid intake Taste alteration	Infections may be viral, fungal, or bacterial in origin.
Radiation therapy	Oral mucositis Xerostomia Infections Taste alterations	Infections generally are fungal or bacterial in nature. Patients receiving radiation therapy are at especially high risk for chronic oral sequelae. Xerostomia may be long-term.
Bone marrow and stem cell transplantation	Oral mucositis Infections Xerostomia Taste alteration Neurotoxicity Temporomandibular dysfunction Dental or skeletal growth and development alterations in children (in conjunction with radiation)	Infections generally are viral, fungal, or bacterial in nature. Frequency and risk depend on overall immune reconstitution. During recovery, patients remain at risk for candidal and herpes simplex virus infections. Xerostomia may be long-term.

Note. Based on information from the National Cancer Institute, 2003.

often is incomplete and the strength of the evidence variable (Clarkson, Worthington, & Eden, 2003).

From a practice standpoint, targeted and well-thought-out interventions are warranted until standards of care are issued. (Guidelines have been published by the Multinational Association for Supportive Care in Cancer in collaboration with the International Society for Oral Oncology.) Toward this end, certain strategies have been identified that are safe and offer symptomatic relief. Additionally, several agents currently are in the research pipeline and are being reviewed. Ultimately, the most effective management strategies may be those that include systemic agents that possess activity against multiple targets.

Strategies currently used for management of mucositis range from oral rinses to antiseptic agents to growth factors (see Table 4). Similar to the assessment process, understanding the biologic process of oral mucositis and the principles of wound care can help to identify specific approaches that may be most beneficial and unlikely to cause additional morbidity.

Bland Rinses

Mouth rinses are used for the prevention and treatment of mucositis. Generally, rinses are used to wash away loose debris and assist with keeping the oral cavity soft and moist (Miller & Kearney, 2001). Safe removal of debris requires that rinses be nonirritating and nondehydrating. The bland rinse category includes 0.9% saline solution, sodium bicarbonate, and a saline and sodium bicarbonate mixture. From the standpoint of a phased stepped approach, normal saline or a saline and sodium bicarbonate mixture commonly is used as a first-line treatment, particularly for patients with minimal risk for developing oral mucositis or those with mild cases. Both are inexpensive and nonabrasive. The addition of saline to sodium bicarbonate makes the rinse more palatable for certain patients and also helps to elevate its pH. Any of the rinses can be administered at room temperature or refrigerated, depending on patient preference (NCI, 2003). Patients should be instructed to take about one tablespoon of solution, swish it around in the oral cavity, and then expectorate; this can be repeated as needed. Based on the current data, bland rinses may be the best choice if one rinse is desired for all phases of mucositis. Commercial mouthwashes containing alcohol are not recommended because of their potential to cause irritation and hypersensitivity.

Cryotherapy

Cryotherapy, which entails the application of ice chips or Popsicles® prior to chemotherapy infusions, is based on the principle of vasoconstriction (i.e., epithelial exposure is reduced) (Kostler, Hejna, Wenzel, & Zielinski, 2001). Although cryotherapy is practical for certain patients (e.g., individuals receiving a bolus of chemotherapy), it is impractical for others (e.g., individuals receiving prolonged chemotherapy infusions). Results of studies in patients receiving 5-fluorouracil have consistently demonstrated significantly lower incidence and severity of oral mucositis (Kostler et al.).

Mucosal Protectants

Mucosal protectants have cytoprotective functions that promote mucosal healing and cell regeneration (Shih, Miaskowski, Dodd, Stotts, & MacPhail, 2002). Various agents include sucralfate suspension, prostaglandin E_2, hydroxypropyl cellulose film (Zilactin®, Zila, Inc., Phoenix, AZ), polyvinylpyrrolidone/sodium hyaluronate (Gelclair®, OSI Pharmaceuticals, Melville, NY), and amifostine. A notable drawback to topical agents, however, is their inability to provide protection to a broad mucosal area. Sucralfate, a basic aluminum salt used in the treatment of gastric and duodenal ulcers, is the most widely studied mucosal protectant. However, evidence supporting its efficacy is fairly weak (Shih et al.). Data from a recent trial demonstrated that patient controls who were administered a salt and soda solution actually healed an average of 13 days sooner (Dodd et al., 2003). Moreover, among the various mucosal protectants (including sucralfate) evaluated in a recent Cochrane meta-analysis, only amifostine was demonstrated to provide a small benefit in terms of risk and severity reduction (Clarkson et al., 2003). Data suggest that the reduction in oral mucositis-related toxicities, which vary depending on the cancer treatment received, may be limited to xerostomia, fibrosis, and loss of taste (Buntzel, Glatzel, Kuttner, Weinaug, & Frohlich, 2002).

Gelclair is a concentrated gel, and Zilactin is a protective film. When applied to the mucosa, both form a protective barrier. Not only do data indicate favorable oral pain control and relatively short onset times, but eating and speaking are facilitated because of the agents' ability to adhere to areas that normally are traumatized by these activities (Buntzel et al., 2002; Smith, 2001; Yamamura et al., 1998). Zilactin, in particular, facilitates the ability to cover the affected area for long time periods (Yamamura et al.).

Table 4. Treatment for Oral Mucositis: Available Agents

Agent	Efficacy	Comments
Bland rinses		
0.9% saline solution	Formal evaluation is lacking.	Relatively innocuous and economical
Sodium bicarbonate	Formal evaluation is lacking.	Creates an alkaline environment that promotes bacterial microflora Unpleasant taste may affect adherence Recommended by the National Cancer Institute
0.9% saline/sodium bicarbonate	Formal evaluation is lacking.	Recommended by the National Cancer Institute
Rinse, multiagent	Data demonstrating efficacy are lacking.	Limited rationale for use Alcohol-based elixirs should be avoided.
Cryotherapy (ice chips)	Consistent reduction in incidence and severity of oral mucositis among patients receiving bolus chemotherapy infusion	Impractical for certain patient groups
Coating agent, mucosal protectant		
Sucralfate suspension	Most data demonstrate no statistically significant difference in oral mucositis severity, pain intensity scores, and other subjective symptoms (e.g., taste alteration, dry mouth).	May offer little or no benefit compared to oral hygiene and symptomatic treatment
Prostaglandin E_2	Studies have produced controversial results. Pilot trials have demonstrated significant reductions in pain and mucositis severity compared to placebo, whereas a smaller randomized clinical trail showed no benefit and higher incidence of herpes simplex virus and severe mucositis. Other treatment-associated adverse events include vomiting, diarrhea, and fever.	Evidence base is insufficient. Further study is needed.
Hydroxypropyl cellulose film	Initial studies are mostly open-label. Certain products may provide some relief for at least three hours. Facilitates ability to cover affected areas over long time periods	Further study is needed. Protective film must remain intact for effectiveness.
Polyvinylpyrrolidone/sodium hyaluronate	Early data demonstrate statistically significant declines in pain scores and improvement in oral mucositis with short onset times.	Further study is needed. Identified as a class 1 medical device. Provides an occlusive dressing for oral lesions
Amifostine	Data suggest marked or significant reductions in mucositis severity compared to placebo or no treatment. Adverse events, including nausea and hypotension, appear to be more pronounced at higher doses.	Optimal dose and route of administration remain to be clarified.
Antiseptic agents		
Chlorhexidine	Overall, data demonstrate no significant change in oral mucositis severity or suppression of any type of oral microflora.	Reports of rinse-induced discomfort, taste alteration, and teeth staining
Hydrogen peroxide	Mixed results. Linked to exacerbation or dryness, stinging, pain, and nausea. Some reports of intensification of symptoms as a result of glossdynia	Long-term use is discouraged. At full potency, it may break down new granulation tissue and disrupt normal oral flora.
Povidone-iodine	Possesses antiviral, antibacterial, and antifungal efficacy. Well-tolerated	Potency limits use in patients with new granulation tissue. Swallowing is contradicted. Further study is needed.
Anti-inflammatory agents		
Kamillosan liquidum rinse	Unfavorable results in clinical trials	Most patients appear to develop mucositis despite treatment.
Chamomile	Lacks data demonstrating its efficacy	Inexpensive, readily available, and innocuous
Oral corticosteroids	No significant difference in degree of mucositis compared to placebo	Data are limited; definitive conclusions cannot be drawn.

(Continued on next page)

Table 4. Treatment for Oral Mucositis: Available Agents *(Continued)*

Agent	Efficacy	Comments
Topical analgesics		
Lidocaine	Limited data. May provide significant relief of limited duration	Requires frequent application, may lead to decreased sensitivity and additional trauma, and may impair taste perception. Prophylaxis not recommended.
Capsaicin	Pilot data demonstrated marked reduction in oral pain.	Clinical potential possibly linked to re-epithelialization and elevation of pain threshold. Further study is warranted.
Topical morphine	May have limited utility. Data suggest reduction in pain severity and duration of pain.	Alcohol-based formulations may cause burning.
Antiproliferative, mucosal protectant, cytokine-like agents and growth factors		
Granulocyte macrophage–colony-stimulating factor	Some data indicate reduction in oral mucositis severity and pain; others do not.	May prove especially beneficial for patients receiving chemotherapy or radiation therapy. High drug discontinuation because of intolerable side effects, including local skin reaction, fever, bone pain, and nausea when administered subcutaneously.
Granulocyte–colony-stimulating factor	Limited data; some indication of significant reductions of oral mucositis severity in bone marrow transplant patients and oral mucositis occurrence in radiation therapy patients when used prophylactically	Further study is needed to draw any conclusion.
Transforming growth factor-ʙ-3	Limited data, mixed outcome. Animal data demonstrate favorable results, but clinical data fail to demonstrate any significant advantage compared to placebo.	Further study is warranted.
Epidermal growth factor	Limited data, animal studies only. In hamsters, linked to worsening of severity and duration of mucositis	Utility in treatment of mucositis appears to be limited.

Note. Based on information from Cerchietti et al., 2002; Clarkson et al., 2003; Foncuberta et al., 2001; Knox et al., 2000; Kostler et al., 2001; Mantovani et al., 2003; Miller & Kearney, 2001; National Cancer Institute, 2003; Redding & Haveman, 1999; Saarilahti e t al., 2002; Shih et al., 2002; Smith, 2001; Sprinzl et al., 2001; Valcarcel et al., 2002.

Multiagent Rinses

Multiagent rinses generally are comprised of a variety of products combined to counteract the various effects of mucositis, including inflammation and pain. Unfortunately, these "mucositis cocktails" (also know as "magic mouthwash") often lack evidence to support their efficacy (Kostler et al., 2001; Shih et al., 2002), and limited rationale exists for their use. Nevertheless, an important rule when using magic mouthwash is to know the ingredients in the cocktail. Alcohol-based elixirs may cause drying, burning, and irritation.

Antiseptic Agents

Antiseptic agents include chlorhexidine, hydrogen peroxide, and povidone-iodine. The initial excitement over chlorhexidine, a second-generation agent characterized by its antimicrobial activity and prolonged action in the oral cavity (Dodd et al., 1996), has been somewhat tempered by inconsistent data demonstrating its efficacy or lack thereof. Moreover, the emergence of gram-negative infections and treatment-induced oral discomfort raises additional doubts about its utility in treating oral mucositis. Data from a double-blind, placebo-controlled trial also demonstrated that chlorhexidine was no more effective than water in terms of incidence, time to onset, and severity of oral mucositis (Dodd et al., 1996). Evidence is similarly mixed for hydrogen peroxide, and its use is discouraged long-term. Although it has some utility as a debriding agent, at full-strength, hydrogen peroxide may break down new granulation tissue and disrupt the normal oral flora (Shih et al., 2002). It also has been linked to exacerbation of dryness, burns, stinging, pain, and nausea (Miller & Kearney, 2001). Similarly, despite povidone-iodine's demonstrable antiseptic activity (which includes antiviral, antibacterial, and antifungal efficacy) and good tolerability (Kostler et al., 2001), its potency also may limit its utility in certain patients (e.g., individuals with new granulation tissue), and swallowing it is absolutely contraindicated (Adamietz et al., 1998). The povidone-iodine solution and swabs commonly used in the clinical setting contain a 10% concentration that should not be used at full strength. Its potential clinical value warrants further investigation.

Anti-Inflammatory Agents

Few agents are directed solely at relieving the inflammatory aspects of oral mucositis. Potential therapies include Kamillosan liquidum rinse, chamomile, and oral corticosteroids. To date, none has yielded significant outcomes (Shih et al., 2002).

However, chamomile, which is the most innocuous and least expensive, appears to possess some antibacterial, antiseptic, and antispasmodic activity and may be beneficial for some patients. Only one study has been published in the mainstream literature comparing chamomile mouthwash to placebo, and the results were inconclusive (Kostler et al., 2001). The efficacy of other alternative herbal essences, including sage, tormentill, and fennel, has not been explored yet (Kostler et al.).

Topical Analgesics

Similar to mucosal protectants, a major drawback of topical analgesics is their inability to provide protection over a large mucosal area. However, for patients who require pain relief in smaller areas, topical anesthetics appear to have some limited utility. Among available agents, which include lidocaine, capsaicin (in a candy base), and topical morphine, all have demonstrated reductions in oral discomfort and temporary pain relief (Cerchietti et al., 2002; Kostler et al., 2001). Capsaicin, which is derived from chili peppers, may exert an effect by promoting re-epithelialization in the mucosal membrane (Berger et al., 1995). It also appears to elevate the pain threshold for areas to which it is applied (NCI, 2003). With regard to morphine, steps should be taken to ensure that the formulation is devoid of alcohol, which can cause burning and drying of the tissues.

Cytokine-Like Agents and Growth Factors

Great interest has been shown in the potential role of cytokine-like agents in mucositis treatment. The anticytotoxic activity of growth factors may inhibit the mucosal response of cancer therapies, promote keratinocyte and fibroblast growth (Shih et al., 2002; Van der Rijt & van Zuijlen, 2002), and facilitate proliferation and differentiation of neutrophil and macrophage lineages, thereby assisting with regeneration and healing. However, similar to agents in other categories, granulocyte–colony-stimulating factor (G-CSF) and granulocyte macrophage–colony-stimulating factor (GM-CSF) administered topically or via mouthwash formulations have demonstrated mixed results in clinical trials and have been shown to be on par with placebo (Knox, Puodziunas, & Feld, 2000; Kostler et al., 2001; Mantovani et al., 2003; Saarilahti, Kajanti, Joensuu, Kouri, & Joensuu, 2002; Sprinzl et al., 2001; Valcarcel et al., 2002). Data suggest that GM-CSF, in particular, might be more effective when used prophylactically than curatively (Clarkson et al., 2003; Mantovani et al.); however, subcutaneous administration has been linked with untoward adverse effects that include application site reactions, bone pain, and fever (Shih et al.).

The data for two additional growth factors, transforming growth factor-b-3 (TGF-b-3, which inhibits epithelial cell division) and epidermal growth factor (EGF, which binds to its epithelial cell receptor and exerts a variety of effects on differentiation, proliferation, and chemotaxis), are limited, and outcomes have been likewise mixed. In hamsters, EGF actually caused a worsening in the severity and duration of mucositis, whereas TGF-b-3 significantly reduced severity and duration (Knox et al., 2000). Clinical studies are warranted. Available phase II clinical data for oral TGF-b-3, administered as a 10 ml rinse four times a day in 116 patients, failed to demonstrate any significant advantage in terms of onset or duration of NCI Common Toxicity Criteria grade 3/4 oral mucositis compared to placebo (Foncuberta et al., 2001).

Agents in the Pipeline

Multiple Activity: EN3247

Several new agents are in late-stage development. EN3247 (triclosan 0.1%) is an oral rinse possessing anti-inflammatory, analgesic, anticytotoxic, and antimicrobial activity. EN3247 targets the cyclooxygenase and lipoxygenase pathways, both of which have been demonstrated to have a role in carcinogenesis, immunosuppression, and inflammation (Steele et al., 1999; Subongkot, Frame, Leslie, & Drajer, 2003). EN3247 has broad-spectrum antimicrobial activity. At bacteriostatic concentrations, it inhibits the uptake of essential amino acids and causes disorganization of the cytoplasmic membrane and cell leakage at bactericidal concentrations (Endo Pharmaceuticals, Inc., 2003). Study data have demonstrated reductions in the occurrence and severity of mucositis. Patients who underwent high mucositis-producing treatment regimens and also received EN3247 experienced an average of 4.6 days of mucositis, compared to 6.12 days of mucositis among patients given a placebo (Goldberg et al., 2002; Goldberg, 2003a). Additionally, data presented at the 2003 American Society of Clinical Oncology (ASCO) annual meeting suggest that EN3247 is well tolerated, with rates of treatment-related adverse effects similar to placebo (EN3247: 24%, placebo: 28%, $p = 0.63$) (Goldberg, 2003b). However, recently released data comparing EN3247 to placebo or saline rinse among 355 patients receiving BMSCT failed to demonstrate statistical significance in terms of the ability to prevent mucositis (Endo Pharmaceuticals, Inc.).

Keratinocyte Growth Factor

Recombinant human keratinocyte growth factor (KGF) is a member of the fibroblast growth factor family. Data suggest that KGF normally is produced by a variety of epithelial cells after injury (Meropol et al., 2003). Administration of recombinant KGF may stimulate proliferation and differentiation of oral epithelial cells and reverse epithelial atrophy in the oral cavity and lower gastrointestinal tract (Dorr, Spekl, & Farrell, 2002; Meropol et al.). Preliminary results of a phase III trial are promising. One hundred and six BMSCT recipients who received KGF three consecutive days before treatment and three days after had significantly fewer days of oral mucositis compared to 106 patients who received placebo (3.7 versus 10.4 days, respectively; $p < 0.001$) (Spielberger et al., 2003). KGF also significantly reduced the incidence of severe oral mucositis: 63% of the patients receiving the drug experienced grade 3/4 oral mucositis versus 98% of patients given placebo ($p < 0.001$) (Spielberger et al.). Patients given recombinant human (rHu)-KGF also required less opioids and total parenteral nutrition. rHu-KGF was well tolerated and improved mouth and throat soreness (Spielberger et al.).

L-Glutamine (AES-14)

Glutamine is one of the most abundant amino acids in the body and appears to be an essential dietary component for supporting and maintaining intestinal growth and function (Okuno et al., 1999). Although earlier trials comparing glutamine supplementation and placebo demonstrated no benefit (Clarkson et al., 2003), preliminary phase III data

presented at the American Society of Clinical Oncology meeting in 2003 suggest that when administered topically to patients undergoing stomatotoxic chemotherapy, AES-14 reduced expression of moderate to severe mucositis by 20% and increased the incidence of grade 0 mucositis by 10% (Peterson & Petit, 2003). AES-14 was well tolerated. Further study is needed to bear out these favorable results.

Benzydamine Hydrochloride

Benzydamine hydrochloride is a multiple-activity agent with anti-inflammatory, anesthetic/analgesic, and antimicrobial properties. Although early evidence of its efficacy is considered weak and unreliable (Clarkson et al., 2003), more recent data suggest that benzydamine rinse significantly reduced erythema and ulceration in 69 patients receiving head and neck radiation therapy and that more than a third of benzydamine subjects remained completely ulcer-free (> 33% versus 18% placebo patients) (Epstein et al., 2001). The agent has been associated with some oral discomfort and is not available commercially in the United States.

Conclusion

Oral mucositis is a common and important side effect of many cancer therapies. No definitive approach to the prevention or treatment of oral mucositis has been identified yet. As knowledge of the biology underlying the development and manifestation of mucositis grows, nurses are provided with the foundation with which to identify innovative management approaches and reduce treatment-related morbidity. Continual assessment and monitoring of high-risk patients are necessary for the effective management of oral mucositis. The systematic use of evidence-based, goal-driven oral care regimens can help reduce the incidence and severity of oral sequelae. Novel therapies for the management of oral mucositis currently are in development, and, ultimately, effective management strategies may broaden to include systemic agents with multiple targets.

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