CLINICAL REVIEW

Henry T. Hoffman, MD, Section Editor

ORAL MUCOSITIS: A CHALLENGING COMPLICATION OF RADIOTHERAPY, CHEMOTHERAPY, AND RATIOCHEMOTHERAPY. PART 2: DIAGNOSIS AND MANAGEMENT OF MUCOSITIS

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Abstract: Background. Oral mucositis is a common sequel of radiotherapy, chemotherapy, and radiochemotherapy in patients with cancer or patients requiring hemopoietic stem cell transplants. Mucositis has a direct and significant impact on the duration of disease remission and cure rates, because it is a treatment-limiting toxicity. Mucositis also affects survival because of the risk of infection and has a significant impact on quality of life and cost of care.

Methods. This article reviews publications on the diagnosis and management of oral mucositis accessible from a MEDLINE search using as key words mucositis, radiotherapy, chemotherapy, hemopoietic stem cell transplant, and oral.

Conclusions. Conventional care of patients with mucositis is currently essentially palliative, with good oral hygiene, narcotic analgesics, and topical palliative mouth rinses. © 2004 Wiley Periodicals, Inc. Head Neck 26: 77–84, 2004

Keywords: cancer; chemotherapy; mucositis; oral; radiotherapy

Mucositis and xerostomia are the most common oral complications of the nonsurgical therapy of cancer. Mucositis is particularly disabling and commonly seen in cancer chemotherapy and almost universally seen after radiotherapy involving the oropharynx. Mucositis is among the most significant major dose-limiting toxicities of intensive cancer therapy and, although specific aspects of mucositis have been reviewed, an overview of the subject is overdue.
Mucositis is a form of mucosal barrier injury or MBI and describes a clinical condition characterized by oral erythema, ulceration, and pain, which is a common complication of a number of therapeutic procedures involving chemotherapy, radiotherapy, or chemoradiotherapy used largely for cancer therapy but also in the conditioning before bone marrow transplantation—hemopoietic stem cell transplantation (HSCT).

Few interventions are of proven efficacy in reducing the severity or duration of mucositis, and there are no universally accepted treatment protocols, but research activity is growing because of the increasing recognition of the importance of mucositis.

MATERIALS AND METHODS
This article reviews publications on the diagnosis and management of oral mucositis accessible from a MEDLINE search to April 2002 using as key words mucositis, radiotherapy, chemotherapy, hemopoietic stem cell transplant, and oral.

RESULTS AND DISCUSSION
Presenting Features of Mucositis. Chemotherapy-induced mucositis typically is seen from 7 to 14 days after the initiation of drug therapy. Radiation-induced mucositis is a function of cumulative tissue dose and typically begins at doses of about 15 Gy to 20 Gy of standard fractionated radiation therapy. Ulcerative mucositis is usually noted at doses of 30 Gy. The typical lesion of advanced mucositis is seen as ulceration, with or without a pseudomembrane, on a bed of erythema. Chemotherapy-induced mucositis is generally limited to nonkeratinized mucosae and most commonly involves the soft palate, ventrum of tongue/floor of mouth, and buccal mucosae. In contrast, radiation-induced mucositis affects those tissues in the radiation field. Consequently, there is no oral mucosal site that is spared. The pain from mucositis is often of such intensity that it can prevent oral intake, necessitate the use of parenteral opioid analgesics, significantly affect quality of life, and result in the interruption of the planned cancer therapy. Although concurrent neutropenia might aggravate the situation and delay recovery, it is not the primary cause of mucositis. The presence of granulocytopenia heightens the patient’s risk of infection, and the presence of mucositis-induced ulceration at a site teeming with microorganisms results in the mucositis being a major primary condition predisposing to bacteremia and sepsis in the myeloablated patient. Interestingly, restoration of the neutrophil count is mirrored in resolution and healing of the mucositis. Typically, resolution of chemotherapy-induced mucositis is noted by 2 to 3 weeks after the administration of the offending drug.

Diagnosis of Mucositis. Diagnosis is clinical and based on the use of known stomatotoxic therapy and the timing and location of oral lesions. Fungal and viral infections and graft-vs-host disease (GVHD) are the most common misdiagnoses in patients at risk for mucositis. Viral infections differ clinically from mucositis in that they are typically croppy, localized, and involve keratinized mucosae of the hard palate, gingiva, and dorsal tongue, and their onset often coincides with fever. In the neutropenic patient in whom there is a question of mucositis or viral infection, culture or exfoliative cytologic studies at the time of lesion presentation are prudent.

GVHD is limited to patients who have received allogeneic HSCT that might develop after hematologic recovery after the transplant and often results in dramatic oral lesions that are often lichenoid in character, sometimes also with xerostomia.

Scoring Mucositis. Scoring the severity of mucositis serves a variety of purposes. Most commonly, a mucositis score is used to measure and convey the toxicity of a particular regimen or drug. Second, scores have been used as a nursing management tool. Finally, mucositis scores are used as end points to determine the efficacy of new treatments for the condition. A number of scoring systems have been devised, but most lack standardization or validation, and, thus far, none have found universal acceptance.

The two most commonly used scoring tools are the World Health Organization (WHO) and the National Cancer Institute (NCI) common toxicity criteria (NCI-CTC). The WHO scale is the most widely used and includes criteria which are objective (presence of erythema and ulceration), subjective (oral pain), and functional (patient’s ability to eat) to determine an overall score. A number of additional scales have been developed to be used as nursing or research tools (Tables 1–5). The choice of mucositis scoring should depend on the specific need of assessment, with different scales used for clinical patient care and for mucositis research. Validation of mucositis scales is required for use in research protocols; one recently validated scale, the Oral Mucositis Assess-
Management Scale (OMAS) has examined utility in a multicenter study, assessing interexaminer and intraexaminer reliability, and it represents the only validated mucositis scale that separates mucosal damage from symptoms and oral function.\textsuperscript{39}

Management of Mucositis. Much of the early interventional trials in mucositis were small, single-center, often nonblinded, nonrandomized protocols, with poorly defined measures of outcome. Even as studies became more sophisticated, progress in the field was hampered by the lack of standardized end points and intrastudy variability of stomatotoxic regimens. As a consequence, a review of the literature often demonstrates conflicting conclusions, with agents seemingly being used to prevent or treat mucositis in similar patient populations. For example, whereas some studies use objective end points requiring frequent oral examination, others are based on patient self-reporting of mucositis severity. A careful, detailed review of the literature is mandatory because of the wide variability in quality of the evidence. Controlled, multicenter, randomized, prospective double-blind studies are needed for progress to be achieved. Much of the literature to date provides suggestions for future studies, but there are few interventions with strong evidence of efficacy.

Prophylactic attempts to minimize mucositis are described in Part I of this article under the specific responsible interventional regimens. Although some controversy exists, it seems that good oral hygiene reduces the severity of oral mucositis and does not increase the risk of bacteremia.\textsuperscript{40} The use of radiation therapy techniques that spare normal tissue, such as IMRT, help to minimize the stomatotoxic effects of therapy by decreasing the area of radiation exposure.

Avoidance of Mucosal Irritation. In general, mucositis should be treated conservatively to avoid further tissue irritation and damaging the remaining cells from which the epithelium will regenerate. Plaque control and oral hygiene should be maintained. The efficacy of chlorhexidine as an adjunct to oral hygiene measures is questionable in mucositis management. Results of recent studies suggest that its value is no more than sterile saline. In the radiated population, there are even some data to suggest that chlorhexidine actually worsens the condition. Patients should be advised to adhere to a soft bland diet, avoiding obvious irritants such as tobacco, alcohol, or spices (Table 6). Nutrition should be maintained with supplements if needed. The use of removable prostheses should be minimized. Orthodontic bands should be removed before the initiation of treatment.

<table>
<thead>
<tr>
<th>Location</th>
<th>Ulceration*</th>
<th>Erythema†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lip Upper</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Lip Lower</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Buccal mucosa Right</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Buccal mucosa Left</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Palate Soft</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
<td>Palate Hard</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
</tbody>
</table>

\textsuperscript{0} = none; \textsuperscript{1} = <1 cm\textsuperscript{2}; \textsuperscript{2} = 1–3 cm\textsuperscript{2}; \textsuperscript{3} = >3 cm\textsuperscript{2}. 
\textsuperscript{10} = none; \textsuperscript{1} = not severe; \textsuperscript{2} = severe.

### Tables

#### Table 1. WHO mucositis scale (WHO 1979).

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Soreness/erythema</td>
</tr>
<tr>
<td>1</td>
<td>Erythema, ulcers but able to eat solids</td>
</tr>
<tr>
<td>2</td>
<td>Ulcers but requires liquid diet</td>
</tr>
<tr>
<td>3</td>
<td>Oral alimentation not possible</td>
</tr>
<tr>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

#### Table 2. Oral mucositis assessment scale (OMAS).\textsuperscript{39}

<table>
<thead>
<tr>
<th>Location</th>
<th>Ulceration*</th>
<th>Erythema†</th>
</tr>
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</tr>
<tr>
<td>Lip Lower</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
<tr>
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<td>Buccal mucosa Left</td>
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<td>0, 1, or 2</td>
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<td>Floor of mouth</td>
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<tr>
<td>Palate Soft</td>
<td>0, 1, 2, or 3</td>
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</tr>
<tr>
<td>Palate Hard</td>
<td>0, 1, 2, or 3</td>
<td>0, 1, or 2</td>
</tr>
</tbody>
</table>

#### Table 3. EORTC/RTOG (Dische) scoring system for mucositis related to radiotherapy.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mucosal response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No reaction</td>
</tr>
<tr>
<td>1</td>
<td>Mild erythema</td>
</tr>
<tr>
<td>2</td>
<td>Severe erythema</td>
</tr>
<tr>
<td>3</td>
<td>Spotted mucositis</td>
</tr>
<tr>
<td>4</td>
<td>Confluent mucositis</td>
</tr>
</tbody>
</table>

#### Table 4. WCCNR (Western Consortium for Cancer Nursing Research) stomatitis scoring system (WCCNR 1998).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Lesions</th>
<th>Color</th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>Pink</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>&lt;4</td>
<td>Slightly red</td>
<td>Not applicable</td>
</tr>
<tr>
<td>2</td>
<td>&gt;4</td>
<td>Moderately red</td>
<td>On eating or oral hygiene</td>
</tr>
<tr>
<td>3</td>
<td>Coalescing</td>
<td>Very red</td>
<td>Spontaneous</td>
</tr>
</tbody>
</table>
Active Treatment of Mucositis. Cryotherapy ice chips placed in the mouth for 5 minutes before bolus administration of 5-FU, and then for a further 25 minutes has been shown in to reduce the mucositis associated with 5-FU chemotherapy.41,42

Benzydamine HCl, an antiinflammatory agent with some action reducing tumor necrosis factor, has demonstrated efficacy in reducing the intensity and duration of mucosal damage and the use of systemic pain relievers, including opioid analgesics,19,43,44 in patients receiving radiation therapy.

Of the many other agents assessed for the treatment of mucositis, topical chlorhexidine gluconate and topical sucralfate have received the most attention. Chlorhexidine is a broad-spectrum topical antiseptic, with considerable oropharyngeal substantivity, that results in up to 12 hours of contact time after topical application. The potential for aqueous chlorhexidine to control chemotherapy-associated oral mucositis was reported by one group,45–47 although no effects on mucositis have been reported from studies at several other centers.48–50 The difference in reported outcome of chlorhexidine on chemotherapy-induced mucositis might be due to differences in study design, sample size in each trial, variable oral hygiene in the studies, possible inactivation of chlorhexidine in the oral environment in some studies, and variable compliance with oral rinses. These findings point to the need for standardized, multicenter, controlled studies, which are complete in reporting compliance with topical agent use. No studies have shown any benefit of chlorhexidine on radiation-induced mucositis.47,51–53 Thus, the potential benefit of prophylactic rinsing with chlorhexidine might be to control plaque levels, gingivitis, reduce caries risk, and oropharyngeal candidiasis rather than any direct effect on oral mucositis.

Although sucralfate, a direct cytoprotectant, was initially thought to have potential benefit both in the management of chemotherapy-induced54–56 and radiation-induced mucositis,57,58 double-blind studies have failed to confirm any efficacy.59,60 Sucralfate is a nonabsorbable aluminium salt of sucrose octasulfate that, when used as a rinse, is only 3% to 5% systemically absorbed. It adheres to ulcer bases, thus creating a surface barrier in the gastrointestinal tract,61–63 has some antibacterial activity,64 and also binds epidermal growth factor and thus might accelerate healing.65 Even in a study that did not show sucralfate to prevent mucositis, oropharyngeal pain was decreased.60 Others have shown the combination of sucralfate with fluconazole to be effective.66

Granulocyte-macrophage colony-stimulating

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### Table 5. Oral Assessment Guide (OAG).

<table>
<thead>
<tr>
<th>Voice</th>
<th>Normal</th>
<th>Deeper or raspy</th>
<th>Difficult talking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swallow</td>
<td>Normal</td>
<td>Some pain</td>
<td>Unable to swallow</td>
</tr>
<tr>
<td>Lips</td>
<td>Smooth pink &amp; moist</td>
<td>Dry or cracked</td>
<td>Ulcerated or bleeding</td>
</tr>
<tr>
<td>Tongue</td>
<td>Pink &amp; moist</td>
<td>Coated &amp; shiny ± red</td>
<td>Blistered or cracked</td>
</tr>
<tr>
<td>Saliva</td>
<td>Watery</td>
<td>Thick</td>
<td>Absent</td>
</tr>
<tr>
<td>Mucous membranes</td>
<td>Pink &amp; moist</td>
<td>Red &amp; coated without ulcers</td>
<td>Ulcers</td>
</tr>
<tr>
<td>Gingivae</td>
<td>Pink &amp; firm</td>
<td>Edematous +/- redness</td>
<td>Spontaneous or pressure-induced bleeding</td>
</tr>
<tr>
<td>Teeth/denture areas</td>
<td>Clean, no debris</td>
<td>Plaque &amp; localized debris</td>
<td>Generalized plaque or debris</td>
</tr>
</tbody>
</table>

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### Table 6. Diet in oral mucositis.

<table>
<thead>
<tr>
<th>Diet that is typically acceptable</th>
<th>Things to avoid</th>
<th>Habits to avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquids</td>
<td>Rough food (potato chips, crisps, toast)</td>
<td>Smoking</td>
</tr>
<tr>
<td>Purees</td>
<td>Spices</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Ice</td>
<td>Salt</td>
<td></td>
</tr>
<tr>
<td>Custards</td>
<td>Acidic fruit (grapefruit, lemon, orange)</td>
<td></td>
</tr>
<tr>
<td>Nonacidic fruits (banana, mango, melon, peach)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft cheeses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eggs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
factor given subcutaneously from days 5 to 14 of chemotherapy might reduce the severity and duration of mucositis induced by a number of chemotherapeutic agents including 5-FU, cisplatinum, cyclophosphamide, doxorubicin, etoposide, methotrexate, vinblastine, and Adriamycin.67–71 Results of clinical trials are conflicting but, when it does seem to be effective, it seems likely to work through a mechanism that is only partially dependent on the marrow-stimulating effect of GM-CSF. Because of conflicting evidence in preliminary studies, controlled studies with mucositis as a primary end point are needed to assess the impact on mucositis.

Control of Pain. Oropharyngeal pain frequently requires systemic analgesics, adjunctive medications, physical therapy, and psychologic therapy in addition to oral care.

Systemic analgesics with nonsteroidal agents and other nonopioids are used first and combined with opioids such as morphine and hydromorphone when pain is severe. In the in-patient setting, patient-controlled analgesia (PCA) provides the most effective pain control with lower total doses of opioid.

Discomfort from established mucositis can be reduced by the following:

- Avoiding oral irritants (smoking, alcohol, or rough or spicy foods)
- Maintaining good oral hygiene
- Using oral cooling with ice chips in patients receiving 5-FU bolus chemotherapy
- Applying topical analgesics to combat pain and dysphagia when used before meals. These include:
  —Anesthetic agents such as lidocaine, dyclonine, or diphenhydramine might give symptomatic relief from the pain of mucositis.52
  —Benzydamine provides topical analgesia and has been shown to reduce the pain, as well as reducing the severity of mucositis in patients receiving radiation therapy.19,43,44
  —Topical doxepin rinse has been shown in preliminary studies to provide prolonged analgesic effect.72
  —Coating agents, including a bioadhesive hydroxypropylcellulose based film (Zilactin),73 also has anti-HSV activity and might be useful for palliation.

Treatment of Oral Infections. Frank oral infections can be seen after cancer therapy and are even more common and severe in patients receiving chemotherapy than after radiotherapy,66,74,75 particularly those related to candidal and herpes simplex virus infections.76 Patients with neutropenia resulting from chemotherapy are at increased risk of septicemia,77–80 particularly involving α-hemolytic streptococci, Candida species, and gram-negative bacteria.81–83 Despite this risk, the use of prophylactic antibacterial therapy is uncommon. In contrast, antifungal prophylaxis, particularly in patients at risk for myeloablation, is common. The use of prophylactic antiviral therapy is common in HSCT.84,85

There has also been considerable interest in the role of yeasts in irradiation mucositis, because Candida species in particular increase during cancer treatment.86,87 Systematic trials with topical or systemic antifungals, however, have consistently failed to prevent the development of, or to improve, irradiation mucositis.47,51,53 Nevertheless, candidiasis is the most common oral fungal infection in cancer patients and might cause mucosal erythema, white plaques, and rarely ulceration and result in oral burning, change in taste, and extend to the esophagus leading to dysphagia and occasionally cause disseminated infections in neutropenic patients.88 Xerostomia, dental prostheses, antibiotics, alcohol use, and tobacco smoking predispose to oral candidiasis in head and neck cancer patients.87 Antifungal prophylaxis is recommended during remission-induction chemotherapy in patients with solid tumors, lymphomas, or leukemias.89 Meta-analysis of numerous studies has shown the prophylactic value of systemic fluconazole89 for Candida albicans, the most frequently pathogenic fungi,90 although topical treatment including nystatin and topical azoles has been disappointing.91,92 Chlorhexidine mouthwashes might also be of value in reducing candidiasis.45,48,50

The significantly increased frequency and severity of oral herpesvirus infections after chemotherapy, radiochemotherapy, and HSCT is well known. The main symptomatic viral infections affecting the mouth in cancer patients are HSV and VZV infections,93 although there are occasional cases reported of cytomegalovirus-induced ulceration.94 Aciclovir and valacyclovir are the most commonly used antiviral agents for HSV or VZV infection, but brivudin and new agents such as famciclovir, penciclovir, bravavir, foscarnet, and others might be needed when there is aciclovir-resistant HSV or other herpes viruses.95
CONCLUSIONS
The current management of oral mucositis in cancer patients remains essentially palliative. The increasing understanding of the etiopathogenesis of mucositis at the molecular level will provide opportunities for continuing study and the development of new and effective interventions. Good-quality, prospective studies are needed.

REFERENCES
75. Bergmann OJ. Alterations in oral microflora and pathogenesis of acute oral infections during remission.