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# S U P P L E M E N T

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## NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care

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### Target Audience

This educational program is designed to meet the needs of advanced practice nurses, medical oncologists, radiation oncologists, and hematologists who treat and manage patients with cancer who experience treatment-induced mucositis.

### Educational Objectives

After completion of this activity, participants should be able to:

- Describe the pathophysiology, clinical manifestations, prevention, and treatment of oropharyngeal mucositis.
- Discuss the early recognition and assessment of oropharyngeal mucositis.
- Identify pharmacologic and non-pharmacologic interventions that can help prevent or mitigate the condition's negative impact on the patient's ability to receive and continue therapy.
- Summarize the scientific evidence underlying the management, including a stage-based approach, of oropharyngeal mucositis secondary to cancer therapy.

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# NCCN Task Force Report

## NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care

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### Key Words

NCCN Task Force Report, mucositis, chemotherapy, radiotherapy

### Abstract

Oral mucositis (OM) has emerged as a common cause of dose delays and interruptions of cancer therapies such as multicycle chemotherapy, myeloablative chemotherapy, and radiotherapy with or without concurrent chemotherapy of head and neck cancer. Research into both preventive and management strategies has lagged behind research into the common cancer treatment-related morbidities of nausea, vomiting, and cytopenias. This disparity is related to the complex risk assessment of multifactorial patient and treatment factors and different techniques of rating mucositis. In addition, relatively few clinical trials have focused on mucositis as a specific outcome. Currently, the only effective preventive strategies include the use of palifermin to prevent OM in the setting of hematopoietic stem cell transplantation and oral cryotherapy used in conjunction with bolus 5-FU, melphalan, or edatrexate. For the most part, managing OM relies on supportive care and symptom palliation. However, OM is a common problem associated with significant patient morbidity and increased resource use. The magnitude of the problem demands innovative approaches based on expert judgment as evidence accumulates to support specific recommendations. To improve this situation, the NCCN convened a multidisciplinary task force to address key issues. This report integrates expert judgment with a review of key literature on risk assessment, prevention, and treatment strategies, and provides recommendations for the overall management of OM. (*JNCCN* 2008;6[Suppl 1]:S1–S21)

### Impact of Oral Mucositis

Until recently, cancer therapy-related nausea, vomiting, and neutropenia were considered the most common complications of cancer therapy, and a variety of new treatment options have emerged over the past several decades. These options include new anti-emetic agents and hematopoietic growth factors, which have dramatically reduced the magnitude of these problems. Mucositis, however, has now emerged as the most significant adverse symptom of cancer therapy reported by patients. Mucositis can affect the entire gastrointestinal tract, and the associated pain and

ulceration can ultimately lead to additional morbidities or even death.<sup>1</sup>

Mucositis can lead to resource-intensive episodes. For example, nutritional resource use increases with the severity of the mucositis; experts estimate that about 22% of patients with solid tumors who have grade 3 to 4 oral mucositis (OM) require total parenteral nutrition (TPN). Ulceration complicating OM provides a portal of entry for microorganisms and frequently leads to systemic infections. In patients with myelosuppression, grade 3 to 4 mucositis is also associated with a 2-fold increase in emergency room visits and an additional 7 days of hospitalization per chemotherapy cycle.<sup>2</sup> In a study performed in the hematopoietic cell transplant (HCT) setting, a 1-point increase in the Oral Mucositis Assessment Scale (OMAS) score was associated with a 3.9-fold increase in 100 day mortality and \$25,405 in additional hospital charges, which rose to \$42,749 if ulcerative mucositis was present.<sup>3</sup>

The goal of cancer therapy is to deliver the full prescribed therapy in a defined timeframe. Therefore, mucositis-associated dose reductions are a source of concern. As reviewed by Elting et al.,<sup>2</sup> clinically significant mucositis will result in a chemotherapy dose reduction in about 23% of cycles, and grade 3 to 4 mucositis will result in a dose reduction in about 28% of cycles. Conversely, radiation-induced mucositis is rarely the cause of dose reductions, which are more commonly associated with skin breakdown, local pain, or difficulty maintaining the airway.<sup>4</sup> When hospital admission is required for patients receiving radiation, however, it is commonly related to mucositis.<sup>4</sup>

Chemotherapy-related mucositis is not limited to the oral cavity but occurs throughout the gastrointestinal tract. However, this discussion focuses on OM, which is mucositis involving the oral cavity, oropharynx, and hypopharynx. This focus reflects that fact that with the

exception of radiation-induced proctitis, most of the literature on mucositis has specifically addressed OM.

### Limitations of Current Research

A reproducible OM scale is a vital prerequisite for both research into preventing and managing OM and routine clinical patient care. A wide variety of scales have been developed. These focus on symptomatic and functional outcomes such as pain or ability to eat, clinical manifestations based on direct inspection of the oral mucosal surfaces, or a combination of both. Each scale has advantages and limitations, and some are more suitable for research (where more objective scales are needed) while others may be more appropriate for clinical management. Additionally, scales have been designed to assess OM in specific cancer treatment settings (radiation therapy, chemotherapy, and HCT). However, variations among these scales hamper data comparison across studies and therapeutic modalities.

Combination endpoint OM scales, such as that from the World Health Organization (WHO), include assessment of mucosal changes, symptoms, and functional assessments. The WHO scale is often used in routine clinical practice, mainly for assessing chemotherapy-related OM, although it has also been used in the transplant setting. Another commonly used scale is the National Cancer Institute–Common Terminology Criteria (NCI–CTC) scale (Common Terminology Criteria for Adverse Events [CTCAE]).

In contrast to the WHO scale, the CTCAE includes separate scales for clinical and functional assessment of mucositis (available at [http://ctep.cancer.gov/reporting/ctc\\_v30.html](http://ctep.cancer.gov/reporting/ctc_v30.html)). The WHO and NCI-CTC scales are summarized in Table 1.

All aspects of OM must be measured, whether for clinical care or research. If OM is assessed using clinical assessment of oral mucosa changes only, the measures will not include OM impact on patient comfort and oral function and separate measures are needed to assess for symptoms and functional alterations. If mucositis pain arises in the throat initially, it may not be possible to directly visualize mucositis. Therefore, a discrepancy may be seen between the patient's functional and symptom status and the assessed clinical mucosal status.<sup>5</sup>

In clinical management settings, a scale that is intuitive and easy to use is important to assure that oral assessments can be consistently applied as part of routine patient care. For example, because interventions are usually triggered by specific events or end points, often reflected by OM score, the different physicians, physician assistants, and nursing staff who routinely examine the mouth need to report the results in a uniform way. This concept is similar to the routine assessment of temperature or blood pressure.

Frequent oral assessments are particularly important in the setting of chemotherapy to detect and monitor OM progression. Nurses or other support staff frequently provide ongoing evaluation during the

**Table 1 Summary of WHO and NCI–CTC Oral Mucositis Scales**

	WHO Scale	NCI–CTC Clinical	NCI–CTC Functional
Grade 1	Oral soreness, erythema	Erythema	Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function
Grade 2	Ulcers but able to eat solids	Patchy ulcerations or pseudomembranes	Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL
Grade 3	Oral ulcers and able to take liquids only	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL
Grade 4	Oral alimentation impossible	Tissue necrosis; significant spontaneous bleeding; life-threatening consequences	Symptoms associated with life-threatening consequences
Grade 5	N/A	Death	Death

Abbreviations: ADL, activities of daily living; N/A, not available; NCI-CTC, National Cancer Institute–Common Terminology Criteria; WHO, World Health Organization.

cycles of chemotherapy, and early recognition of worsening OM can be used to initiate physician assessments and subsequent prescription of appropriate medications. Even patients and their families can be trained to recognize the signs and symptoms of incipient OM, thus enabling better communication about the patient's status and prompting more timely care.

The Oral Assessment Guide (OAG) is an example of a scale developed for routine use by nurses and other support staff. Eight different aspects of the oral cavity are assessed and assigned a point value from 1 to 3 based on whether these aspects are normal or show moderate to severe changes. This scale is primarily used to monitor patient status and trigger interventions when oral health worsens. However, the key issue is to consistently use an accepted grading scale throughout treatment. The WHO scale is the most commonly used scale in the published literature.

An important aspect of overall management is consideration of both therapy- and patient-related risk factors for OM. The ability to identify patients at higher risk for OM allows for closer scrutiny for oral changes and symptoms related to OM and thus can help both patients and physicians anticipate the need to start OM treatment in a more timely manner. Clearly, the most important risk factor for OM is the cancer therapy being administered, including type of therapy (chemotherapy, radiation, or combined chemoradiotherapy), dosage, and delivery schedule. For patients undergoing high-dose therapy and allogeneic HCT, the risk for mucositis is primarily related to the conditioning regimen. For example, the dose and schedule of chemotherapy with or without total body irradiation (TBI) is related to the severity of OM. Additionally, if methotrexate is used in the first several weeks after HCT to prevent acute graft versus host disease (GVHD), it can predictably increase the severity of OM. Although different chemotherapy regimens have been classified according to their emetogenicity, classification of OM risk has lagged behind.

The multifactorial nature of risk assessment is challenging. OM research suggests that genetic differences (polymorphisms) that alter responses to cancer chemotherapy and radiation may be another important risk factor for OM.<sup>6,7</sup> Additionally, risk for OM may vary according to patient age, comorbidities, type of malignancy, and original oral health. Furthermore, a steady stream of new drugs has entered the marketplace, including anti-angiogenic agents and other

targeted therapies. Although these drugs may not be associated with mucositis on their own, the risk for OM may be affected when new drugs are combined with other regimens. Unfortunately, OM endpoints have not been routinely included in phase II and III trials of new drugs and regimens. Furthermore, objective OM outcomes have been difficult to define and are subject to physician bias. Therefore, systematic evaluation and characterization of factors critical to assessing OM risk are needed to identify individuals most susceptible to this serious and disruptive adverse event.

### Limitations of Existing Meta-Analyses and Guidelines

Reviews, management strategies, and clinical guidelines have been published recognizing the clinical importance of OM. In 2006, Worthington et al.<sup>8</sup> published a Cochrane review that specifically focused on randomized clinical trials addressing OM with the goal of providing a point estimate of benefit. This review included 71 trials of 29 different interventions; 35 addressed head and neck cancer, 5 leukemia, 15 solid tumors, and 12 hematologic and solid tumors. In this analysis, only 4 interventions for prevention showed any benefit: ice chips, antibiotic paste, amifostine, and hydrolytic enzymes.

That review illustrates the limited number of well-researched options for OM prevention. However, the NCCN Task Force noted several methodologic limitations. For example, the meta-analysis focused only on the incidence of OM and not on other important aspects, such as duration. Although incidence is obviously important, any therapy that could reduce the duration of OM is equally important. Additionally, the meta-analysis did not control for the variety of ways that OM was assessed across the reviewed studies. Finally, a meta-analysis focusing only on randomized studies is an informative methodology for a mature field that includes a large number of well-designed clinical trials, such as studies on antiemetics or antibiotics for neutropenic fever. In contrast, because OM is an emerging area of research with few well-designed clinical trials, it is not well suited to meta-analysis. The paucity of literature is not surprising given that OM has not been routinely included as a specific outcome in chemotherapy or radiation therapy clinical trials.

Other methodologies are needed to review and summarize the scientific literature, such as using other types of evidence (e.g., phase II trials, single-arm trials) and, where research does not exist, expert judgment.

The Multinational Association of Supportive Cancer Care (MASCC) recently updated guidelines for preventing and treating OM (Table 2). The MASCC guidelines are based on an evidence-based review of

published literature to provide recommendations and suggestions for individual agents for patients receiving radiotherapy or standard or high-dose chemotherapy.<sup>9</sup> In addition, the guidelines indicate which agents should

<b>Table 2 Guidelines from the Multinational Association of Supportive Cancer Care for Management of Patients with OM*</b>
<b>Basic Oral Care and Clinical Practices</b>
<ol style="list-style-type: none"> <li>1. The panel suggests multidisciplinary development and evaluation of oral care protocols and patient and staff education in the use of such protocols to reduce the severity of OM from chemotherapy and/or radiation therapy. As part of the protocols, the panel suggests the use of a soft toothbrush on a regular basis. Elements of good clinical practice should include the use of validated tools to regularly assess oral pain and oral cavity health. The inclusion of dental professionals is vital throughout the treatment and follow-up phases.</li> <li>2. The panel recommends patient-controlled analgesia with morphine as the treatment of choice for OM pain in patients undergoing HCT. Regular oral pain assessment using validated instruments for self-reporting is essential.</li> </ol>
<b>Radiotherapy: Prevention</b>
<ol style="list-style-type: none"> <li>3. The panel recommends the use of midline radiation blocks and 3-dimensional radiation treatment to reduce mucosal injury.</li> <li>4. The panel recommends benzydamine to prevent radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy.<sup>†</sup></li> <li>5. The panel recommended that chlorhexidine not be used to prevent OM in patients with solid tumors of the head or neck who are undergoing radiotherapy.</li> <li>6. The panel recommends that antimicrobial lozenges not be used to prevent radiation-induced OM.</li> </ol>
<b>Radiotherapy: Treatment</b>
<ol style="list-style-type: none"> <li>7. The panel recommends that sucralfate not be used to treat radiation-induced OM.</li> </ol>
<b>Standard Dose Chemotherapy: Prevention</b>
<ol style="list-style-type: none"> <li>8. The panel recommends that patients receiving bolus 5-FU chemotherapy undergo 30 minutes of oral cryotherapy to prevent OM.</li> <li>9. The panel suggests the use of 20–30 minutes of oral cryotherapy to decrease mucositis in patients treated with bolus doses of edatrexate.</li> <li>10. The panel recommends that acyclovir and its analogues not be used routinely to prevent mucositis.</li> </ol>
<b>Standard-Dose Chemotherapy: Treatment</b>
<ol style="list-style-type: none"> <li>11. The panel recommends that chlorhexidine not be used to treat established OM.</li> </ol>
<b>High-Dose Chemotherapy (With or Without TBI) Plus HCT: Prevention</b>
<ol style="list-style-type: none"> <li>12. In patients with hematologic malignancies who are receiving high-dose chemotherapy and TBI with autologous stem cell transplantation, the panel recommends the use of keratinocyte growth factor-1 (palifermin) in a dose of 60 mcg/kg/day for 3 days before conditioning treatment and for 3 days after transplantation to prevent OM.</li> <li>13. The panel suggests the use of cryotherapy to prevent OM in patients receiving high-dose melphalan.</li> <li>14. The panel does not recommend the use of pentoxifylline to prevent mucositis in patients undergoing HCT.</li> <li>15. The panel suggests that granulocyte-macrophage colony-stimulating factor mouthwashes not be used to prevent OM in patients undergoing HCT.</li> <li>16. The panel suggests the use of LLLT to reduce the incidence of OM and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HCT if the treatment center is able to support the necessary technology and training, because LLLT requires expensive equipment and specialized training. Because of interoperative variability, clinical trials are difficult to conduct, and their results are difficult to compare; nevertheless, the panel is encouraged by the accumulating evidence to support LLLT.</li> </ol>

\*Adapted from Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007;109:820–831; with permission. Copyright © 2007 American Cancer Society.

†The NCCN panel members disagreed about the value of benzydamine in the prevention of mucositis secondary to radiation therapy. Abbreviations: HCT, hematopoietic stem cell transplantation; LLLT, low-level laser therapy; OM, oral mucositis; TBI, total body irradiation.

not be used based on the level of proof or where consensus is lacking regarding the agents' efficacy for mucositis versus benefit for other aspects of oral health. For example, acyclovir should be used to prevent reactivation of the Herpes simplex virus in immunosuppressed patients but not to prevent mucositis.

Despite these important evidence-based guidelines, the lack of comprehensive research on all management modalities for OM makes recommendations for comprehensive management across all clinical settings necessary. These recommendations should combine consideration of patient- and treatment-related risk factors with pharmacologic and nonpharmacologic management strategies. In the subsequent sections, the NCCN Task Force Report discusses overall management strategies for preventing and treating OM based on the evaluation of available data, the Cochrane review, and the MASCC guidelines, integrated with the expert judgment of the Task Force members.

### Consideration of Treatment-Related Risk Factors

In OM, treatment-related factors are the most important. Therefore, these factors should be assessed before cancer therapy is started. The time course and range of severity of OM vary with treatment. Therefore, risk assessment is discussed separately for multicycle chemotherapy, myeloablative chemotherapy in the HCT setting, and radiation therapy for head and neck cancer.

#### Multicycle Chemotherapy

The availability of literature focusing directly on OM risk is lacking, but the results of clinical trials on the effectiveness of chemotherapy also report data on OM. Table 3 summarizes the risks of grade 3 or 4 mucositis associated with different chemotherapy regimens.

As the intensity of therapy increases, so does the risk for OM. Agents with the highest OM risk include cisplatin, 5-FU, methotrexate, and cyclophosphamide. OM risk also varies across chemotherapy cycles. Cycles of myelosuppressive chemotherapy can have a cumulative effect, and the risk of OM appears to increase with subsequent cycles if it has occurred in the previous cycle. Notably, adding radiation to chemotherapy and vice versa increase the risk of developing OM. This has been noted in mucositis studies in HCT patients who are conditioned with or without TBI. More

strikingly, the risk of OM approaches 100% in patients with head and neck cancer who receive intensive chemoradiation.

The data in Table 3 are derived from clinical trials. However, the risk for OM may be higher in routine practice, in which a broader range of patients is treated than usually participate in clinical trials, such as patients who are less adherent to medication schedules, more elderly patients, or patients with more comorbidities.

#### Myeloablative Therapy and HCT

Mucositis is common in the transplant setting, with severity primarily related to the conditioning regimen used. As previously stated, acute GVHD prophylaxis with methotrexate also contributes to mucositis. Additionally, clinicians should recognize that mucositis in the setting of myelosuppression increases the risk of sepsis. One reported study compared the incidence of OM in 365 patients who underwent stem cell transplantation after different conditioning regimens. Although mean OM scores varied according to conditioning regimen used, the time course of OM was somewhat consistent, showing a peak between 6 and 12 days after HCT and then slowly resolving over the next 7 to 14 days. The authors of a multivariate analysis found that the conditioning regimen was the only independent risk factor for OM.<sup>10</sup>

Robien et al.<sup>11</sup> studied the severity of OM in 133 patients with chronic myelogenous leukemia undergoing either TBI or a busulfan-based conditioning regimen before undergoing allogeneic transplantation. Patients also received 4 doses of methotrexate after transplantation for GVHD prophylaxis. These authors reported a greater risk of OM among patients receiving TBI, those with a pretransplantation body mass greater than 25, and those receiving methotrexate GVHD prophylaxis who had a genetic polymorphism of the *MTHFR* gene that resulted in slow metabolism of methotrexate.

Data is inconsistent regarding the comparative OM risk associated with allogeneic versus autologous transplant,<sup>12</sup> but studies have reported conflicting results.<sup>13,14</sup> Methotrexate use for GVHD prophylaxis early after HCT will increase the risk of OM in allogeneic HCT patients. However, when a calcineurin-inhibitor and other immunosuppressive agents are used for GVHD prophylaxis, a lower mucositis risk is noted. Cutler et al.<sup>15</sup> compared the incidence of mucositis in

## NCCN Task Force Report

Table 3 Risk of Grade 3 or 4 Oral Mucositis by Chemotherapy Regimen*				
Regimen	Number		Risk of Grade 3-4 Oral Mucositis	
	Studies	Patients	%	CI
<b>All NHL</b>	19	1444	6.55	5.54–8
NHL-15 (NHL regimen 15)	1	100	3.00	0.50–7
CHOP-14 (cyclophosphamide, doxorubicin, vincristine, prednisone)	9	623	4.82	3.53–6.78
CHOP-DI 14 (as CHOP, but dose intensified)	4	231	7.85	5.28–11.32
CHOEP-14 (cyclophosphamide doxorubicin, vincristine, etoposide, prednisone)	2	346	10.4	7.23–13.44
CEOP/IMVP-Dexa (cyclophosphamide, etoposide, vincristine, prednisone/ ifosfamide, methotrexate-dexamethasone)	3	144	4.17	1.74–7.99
<b>All Breast</b>	21	2766	4.08	3.44–4.85
A→T→C (sequential doxorubicin, taxane, cyclophosphamide)	4	594	2.29	1.30–3.46
AC→T (sequential doxorubicin, cyclophosphamide, taxane)	2	515	2.80	1.40–4.20
A→CT (sequential doxorubicin, cyclophosphamide, taxane)	1	19	5.26	2.63–15.79
A→T (sequential doxorubicin, taxane)	2	60	4.17	1.67–10
AT (doxorubicin and taxane)	1	36	8.33	1.39–19.44
FAC (weekly 5-FU, doxorubicin, cyclophosphamide)	1	30	3.33	1.67–10.00
AC (weekly doxorubicin and cyclophosphamide)	1	22	13.64	2.27–27.27
Taxol (weekly paclitaxel)	2	87	2.87	1.15–6.90
TAC (docetaxel, doxorubicin, cyclophosphamide)	7	1403	4.92	3.83–6.07
<b>All Lung (Without Radiation)</b>	49	4750	0.79	0.88–1.33
Platinum, paclitaxel	16	2009	0.49	0.52–1.06
Platinum, paclitaxel (low dose)	1	49	1.02	1.02–4.08
Platinum, docetaxel	1	38	1.32	1.32–5.26
Platinum, paclitaxel, other	7	451	1.47	1.20–3.07
Platinum, docetaxel, other	1	83	0.60	0.60–2.41
Gemcitabine, platinum	18	1476	1.08	0.09–1.91
Gemcitabine, paclitaxel	2	109	1.84	1.02–5.33
Gemcitabine, vinorelbine	1	67	0.75	0.75–2.99
Vinorelbine, paclitaxel	1	175	0.29	0.29–1.14
Vinorelbine, platinum	1	203	0.25	0.25–0.99
<b>All Colon</b>	10	898	1.67	1.17–2.67
FOLFOX (5-FU, leucovorin, oxaliplatin)	5	482	1.35	0.73–2.59
FOLFIRI (5-FU, leucovorin, irinotecan)	2	79	4.43	1.90–9.49
IROX (irinotecan, oxaliplatin)	3	337	1.48	0.59–2.97

\*Adapted from Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer* 2007;109:820–831; with permission. Copyright © 2007 American Cancer Society. Abbreviations: CI, confidence interval; NHL, Non-Hodgkin's Lymphoma.

2 cohorts of patients receiving either sirolimus or methotrexate prophylaxis. All grades of mucositis were decreased in the group receiving sirolimus. Other outcomes were improved in this group as well, including number of TPN days, days requiring narcotics, and time to first hospital discharge.

### Radiation Therapy for Head and Neck Cancer

Radiation therapy to the oral cavity induces OM. Its extent and severity depends on the total dose, fraction size, volume irradiated, overall treatment time, and fractionation regimen (e.g., hyperfractionated or accelerated schedules). Concurrent chemotherapy will increase the risk for OM. OM from radiotherapy peaks at about weeks 5 to 6 and typically resolves during weeks 8 to 12 of follow-up.<sup>16</sup> In a retrospective study of 450 patients with head and neck cancer treated with radiotherapy, 29% developed grade 2 to 3 OM, which was associated with nasopharyngeal or oropharyngeal tumors, a cumulative radiation dose of greater than 5000 Gy, or the use of concomitant chemotherapy.<sup>17</sup> In a meta-analysis, Trotti et al.<sup>4</sup> compared the incidence of grade 3 or 4 OM in patients with head and neck cancer treated with conventional radiation, accelerated radiation, or chemoradiation as routinely reported secondary endpoints in cancer therapeutic clinical trials. The results are summarized in Table 4.

As noted, a high incidence of severe OM is associated with any type of radiotherapy for head and neck cancer, with an increased risk associated with both accelerated schedules and the addition of chemotherapy. Mucositis intervention trials focusing on this injury as a primary endpoint show even higher rates.

### Consideration of Patient-Related Risk Factors

Clearly, patient factors play an important role in OM risk, given the variable response of individual patients

to the same treatment regimen. The most common factors studied are age, gender, nutritional status, comorbidities, and dentition.

Experts initially assumed that age would be a poor risk factor, perhaps mediated through impaired renal function and declining stem cell reserve in older populations. However, studies on the influence of age on OM have produced inconsistent results, possibly because not many protocols are used across a large enough age range to allow for adequate comparisons. For example, one large retrospective study of patients with head and neck cancer treated with radiation therapy suggested that older age was a protective factor.<sup>17</sup> In contrast, older age appears to be an adverse factor in patients receiving 5-FU for solid tumors, particularly cancer of the gastrointestinal tract. Zalcberg et al.<sup>18</sup> studied 439 patients enrolled in a phase III trial comparing raltitrexed (a novel thymidylate synthase inhibitor) and 5-FU with leucovorin. Grade 3 or 4 leukopenia and OM were significantly correlated with age (especially > 70 years) only in patients receiving 5-FU. Finally, in a large case series of patients undergoing either allogeneic or autologous stem cell transplant, Wardley et al.<sup>10</sup> performed a multivariate analysis of the risk factors for OM and found that age was not a predictive factor.

Data regarding the impact of gender on OM are more consistent, showing a significantly greater risk of OM in women compared with men. Vokurka et al.<sup>19</sup> studied the impact of gender on the incidence of OM as part of a randomized trial comparing therapeutic mouthwashes in 148 patients undergoing autologous stem cell transplantation. OM occurred significantly more often in women than in men (86% vs. 60%) and was more severe and of longer duration. Similarly, women receiving 5-FU appear to be at higher risk for OM. In an analysis of 4 colorectal cancer trials of 5-FU-containing regimens including 1074 patients, Chansky et al.<sup>20</sup> reported that, compared with men, women had a significantly higher average toxicity grade and incidence of toxicity grade 2 or higher. The authors concluded that these data supported gender differences in 5-FU toxicity seen across a range of treatment regimens, patient characteristics, and cancer trial settings. In contrast, gender was not found to be a predictor of OM in a study of 133 patients undergoing allogeneic transplantation or in a large survey of patients receiving radiation therapy for head and neck cancer.<sup>11,17</sup> However, the data

**Table 4 Incidence of Grade 3–4 Oral Mucositis\***

Treatment	Patients, n	Incidence, %
Conventional RT	2875	34
Accelerated RT	1096	57
Chemoradiation	1505	43

\*Adapted from Trotti A, Bellem LA, Epstein JB, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiation Oncol* 2003;66:253–262; with permission from Elsevier. Abbreviation: RT, radiation therapy.

regarding radiation therapy are not definitive, and a greater gender difference might be associated with increased intensity of treatment, which was probably not reflected in this survey.

Data on ethnicity and mucositis suggest that African-Americans treated with 5-FU for colon cancer experience less mucositis than Caucasians.<sup>21</sup> McCollum et al.<sup>21</sup> reviewed the experience of 344 African-Americans and 3036 Caucasians with similar access to health care. Although the disease-free and overall survivals were not related to ethnicity, African-Americans experienced statistically lower rates of mucositis.

Although nutritional status and weight are assumed to have an impact on OM risk, this issue has been difficult to study because nutritional status may be a surrogate for other co-morbidities. In their review of 133 patients with chronic myelogenous leukemia undergoing allogeneic transplantation, Robien et al.<sup>11</sup> reported that a body mass index (BMI) greater than 25 was associated with an increased risk for OM. The authors hypothesize that the causative factors might be higher chemotherapy doses when based on BMI or altered pharmacokinetics related to an increased ratio of adipose tissue to lean body weight. In contrast, a retrospective, multivariate analysis of 150 patients with various solid tumors treated with chemotherapy reported that a low body weight was associated with an increased risk of OM.<sup>22</sup> However, the large case series of radiation therapy reported by Vera-Llonch et al.<sup>17</sup> did not show body weight, high or low, to be associated with incidence of OM.

Salivary gland dysfunction (hypofunction) is a well-documented side effect of head and neck radiation therapy, but it is less well understood relative to chemotherapy protocols. In addition, small studies have suggested that oral dryness may contribute to OM. Although not clear, experts believe that the loss of saliva indirectly influences OM by several mechanisms: 1) increased trauma and irritation caused by loss of surface lubrication of tissues; 2) unfavorable influences on microbial colonization; and 3) dehydration of mucosal surfaces. For example, McCarthy et al.<sup>23</sup> followed up 63 patients receiving 5-FU for gastrointestinal malignancies with patient-administered questionnaires, oral examinations, and salivary flow measurements. Analysis showed that OM was significantly associated with salivary gland

hypofunction at baseline and during chemotherapy. Salivary gland dysfunction is a side effect of many medications including anticholinergics, antihypertensives, and antidepressants. For example, in the previous study, 25% of patients were taking drugs that caused salivary gland hypofunction, suggesting that all medications should be reviewed and substitutions made if possible.

Trauma and irritation caused by dentition and oral function is another patient-related risk factor that is potentially modifiable. For example, non-keratinized oral mucosal surfaces in dentate patients appear to be at higher risk for OM in general than in edentulous patients with dentures. Furthermore, constant physical trauma related to eating, ill fitting dentures, or sharp or fractured teeth for patients receiving chemotherapy or radiation appears to put the oral cavity at higher risk for additional mucosal trauma, thus worsening the expression of OM. Recommending that patients avoid rough-textured foods while receiving cancer treatments and for the time period of highest risk may be reasonable.

Dental health may also impact the risk of sepsis from periodontal tissues regardless of the presence of OM, particularly if the anticancer regimen is associated with myelosuppression. Bacterial dental plaque may possibly contribute to local bacterial invasion of ulcerative mucositis lesions. Dentition-related risk factors can be easily assessed during a careful dental examination, which is recommended in all patients. Even edentulous patients should be evaluated for retained root tips that may become a nidus for infection after myelosuppression. Fractured or sharp teeth or restorations should be repaired before treatment. Dental infections should be stabilized. Transplant centers should establish a relationship with dentists to evaluate and treat patients quickly; this is particularly acute for leukemic patients who may require emergent treatment.

Dental appliances, including removable dentures, retainers, and orthodontic bands, can contribute to mucosal trauma and the aggravation of OM. Therefore, dental appliances should be carefully evaluated before therapy; advising patients to minimize wearing dental appliances is another consideration. Generally, patients at significant risk for mucositis (especially HCT patients) should be advised to remove orthodontic bands before the start of treatment.

## OM Preventive Strategies

### Oral Hygiene

Effective oral hygiene is a universal preventive strategy and should be considered part of “good clinical practice.” A growing body of evidence supports the value of reducing bacterial dental plaque relative to reducing OM, but further research is clearly needed. As noted in the MASCC guidelines, effective oral hygiene includes brushing with a soft brush twice a day, flossing once a day, and frequent rinsing with bland rinses and oral moisturizers to address potential salivary gland dysfunction. Bland rinses typically include 0.9% saline, sodium bicarbonate solutions, and water. The temperature of the rinse can be varied based on patient desires. Moderate xerostomia can also be managed with products to stimulate salivary gland function through the sense of taste or with medications (listed in Figure 1). No one rinse has been shown to be superior; therefore, the choice is based on clinical assessment and patient preference.<sup>24</sup> Patient medications should be reviewed to identify those associated with salivary gland dysfunction and efforts should be made to substitute these drugs with agents not associated with it.

### Topical Therapies

A variety of topical modalities have also been long suggested for OM prevention and management. However, with the exception of cryotherapy, supportive data are largely inconclusive or not available.

Preventive oral cryotherapy (ice-chip therapy) is a strategy used in patients receiving bolus stomatotoxic chemotherapy agents with relatively short half-lives. Patients are instructed to continually hold ice chips in the mouth starting before the administration of the chemotherapy and then for up to several hours after drug infusion. This has been hypothesized to cause local vasoconstriction that reduces drug delivery to oral mucosal tissues and thus reduces the risk of OM. Oral cryotherapy has been investigated in 3 settings: high-dose melphalan before HCT, bolus 5-FU, and bolus edatrexate. In these settings, randomized studies have reported a positive preventive benefit.

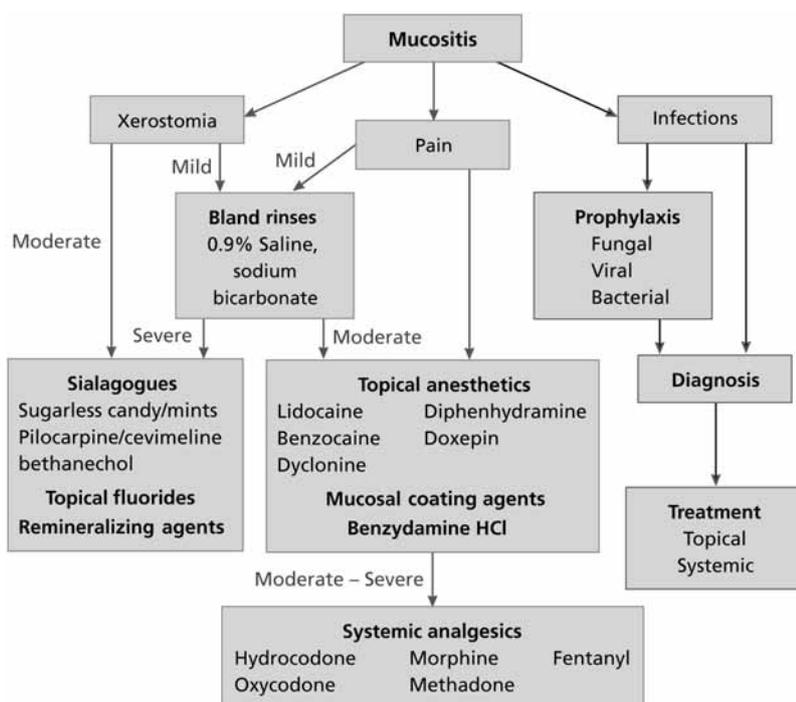
Lilleby et al.<sup>25</sup> reported on a trial randomizing 40 patients with multiple myeloma treated with high-dose melphalan to receive either saline or cryotherapy 30 minutes before and 6 hours after therapy. Compared with the normal saline group, patients using cryotherapy experienced less grade 3 to 4 OM (14% vs. 74%),

a lower use of narcotics, and lower use of TPN. Another randomized study compared cryotherapy and standard oral care in 80 patients undergoing a variety of conditioning regimens followed by either autologous or allogeneic transplant.<sup>26</sup> This trial specifically examined opioid use as a surrogate outcome of OM severity and reported that cryotherapy was associated with significantly fewer days of intravenous opioid use compared with the control. In the autologous setting, cryotherapy patients also needed significantly lower total doses of opioids.

Two other small studies have also supported the beneficial effect of cryotherapy.<sup>27,28</sup> Although the timing and duration of cryotherapy differed among these and other small studies, the results consistently support the role of cryotherapy as a preventive measure in patients receiving high-dose melphalan.<sup>27,28</sup> Some institutions have anecdotally reported that, when properly used, cryotherapy has significantly reduced the hospitalization related to melphalan-induced OM in autologous HCT patients and that oral cryotherapy is now standard therapy for anyone receiving high-dose melphalan.

Two randomized studies reported that 30 minutes of cryotherapy can prevent severe OM in patients receiving 5-FU.<sup>29,30</sup> Notably, cryotherapy will only prevent OM when the drug regimen has a short duration of action. Therefore, although cryotherapy can be effective with 5-FU alone, it will be less effective or ineffective in combination regimens, such as FOLFOX, in which oxaliplatin has a longer duration of action. Finally, some patients may have difficulty tolerating this duration of cryotherapy unless specifically encouraged and motivated. Compliance may also be more challenging in the setting of multicycle chemotherapy compared with a single cryotherapy treatment for transplant.

Although disinfective mouthwashes, antibiotic rinses, pastilles, or lozenges have been used in HCT and myelosuppression to reduce the risk of infection, only weak or conflicting data support an effect on OM incidence.<sup>31–38</sup> Similarly, weak data support the use of oral zinc sulfate supplementation or chlorhexidine.<sup>39,40</sup> MASCC guidelines specifically recommend that chlorhexidine not be used to prevent OM. These treatments are best reserved for oral hygiene protocols attempting to reduce bacterial colonization of mucosal and periodontal tissues. Patients have variable tolerance of different oral rinses. Therefore, given the lack



**Figure 1** For most patients at risk for oral mucositis, management involves palliation of symptoms with bland rinses, topical anesthetics, mucosal coating agents, and analgesics. Strategies to manage salivary gland dysfunction and prevent infectious complications can further decrease patient discomfort and improve oral function. Courtesy of Mark Shubert, DDS, MSD.

of compelling data, the choice should be driven by clinical assessment and patient preference.

Various preparations of topical and systemic glutamine have been studied over the years. However, study results have been very inconsistent. More recently, a phase III randomized trial investigated a glutamine suspension using a proprietary delivery system designed to enhance glutamine absorption across the oral mucosa (Safaris, MGI Pharma, Bloomington, MN). A total of 326 patients with breast cancer with a history of grade 3 or higher mucositis in a previous anthracycline-based chemotherapy cycle were randomized to receive either glutamine suspension or placebo in their next cycle.<sup>41</sup> The incidence of grade 3 or 4 OM in the treatment group was 1.2% compared with 6.7% in the placebo group. The FDA has given Safaris an approvable letter for OM, but is requiring the manufacturer to do a new phase III trial before a full approval is made.

### Parenteral Agents

Palifermin, a keratinocyte growth factor, is currently the only drug to be FDA-approved specifically for

the prevention of chemotherapy-induced OM. The labeled indication states that palifermin is indicated for managing severe OM in patients with hematologic malignancies receiving myelotoxic therapy requiring HCT. This drug increases the thickness of the mucosal epithelium; upregulates genes encoding for scavenging enzymes targeting reactive oxygen species; stimulates IL (interleukin)-13, thereby reducing tumor necrosis factor-alpha; and reduces angiogenesis and apoptosis.

FDA approval of palifermin was based in part on the results of a randomized double-blind phase III trial focusing on its use in the setting of stem cell transplant preceded by a TBI-containing conditioning regimen. The trial enrolled 212 patients with hematologic malignancies who were randomized to receive either placebo or palifermin 3 days before conditioning irradiation and 3 days after autologous stem cell transplantation.

<sup>42</sup> The incidence of grade 3 or 4 OM was 63% in the palifermin group compared with 98% in the placebo group. Although a high incidence of any grade of OM was still found in both groups, these results suggest that palifermin can reduce grade 3 and 4 OM. For example, the incidence of grade 4 OM alone was 20% in the palifermin group compared with 62% in the placebo group. The duration of grade 3 or 4 OM was 3 days in the palifermin group compared with 9 days in the placebo group. These outcomes resulted in reduced use of opioids and reduced need for TPN. Adverse events were minimal, most notably a transient skin rash, mucosal changes, altered taste sensation, and thickened tongue. Patient-reported outcomes, including assessment of mouth and throat soreness and functional activities (such as eating, drinking, and swallowing) also improved.<sup>43</sup> A retrospective analysis of the hospital costs suggested that reductions in adverse outcomes and their associated hospital stay offset the acquisition price of palifermin.<sup>44</sup>

Although the pivotal trial only enrolled patients receiving TBI as part of the conditioning regimen, the FDA labeling for palifermin is broader and includes patients receiving myelotoxic therapy and stem cell support. Preliminary data in patients receiving non-TBI-containing regimens consistently suggests that palifermin can reduce the incidence and severity of OM. For example, Luthi et al.<sup>45</sup> treated 34 patients with palifermin before high-dose therapy with melphalan or the BEAM regimen. The authors reported that 17% of patients treated with palifermin experienced grade 2 or higher OM compared with 44% in a historical control group.

In another small case series, Kobbe et al.<sup>46</sup> studied palifermin in 15 patients with multiple myeloma receiving high-dose melphalan, compared with a contemporary control of 21 patients receiving only granulocyte-macrophage colony-stimulating factor. A significant reduction in the incidence and severity of OM and a 3-day reduction in the duration of hospitalization was seen in the palifermin group.

Minimal data are available regarding palifermin in allogeneic transplantation. Concern has been raised that palifermin may reduce the “graft versus leukemia” effect, which reduces the risk of post-transplant relapse. Blazar et al.<sup>47</sup> reported the results of a phase I and II trial of palifermin in patients undergoing TBI-based conditioning for an allogeneic HCT. In this double-blind, placebo-controlled trial, 69 patients undergoing allogeneic transplant with GVHD prophylaxis received either placebo or 1 of 2 different doses of palifermin. Palifermin was associated with reduced incidence and mean severity of OM in patients receiving TBI-based conditioning regimens, but not in those receiving busulfan-based conditioning. No significant differences were seen in other outcomes. The authors concluded that palifermin was generally safe in the setting of allogeneic transplant and had no significant adverse effect on engraftment, acute GVHD, or survival in this trial.

Because of the limited experience with the safety of palifermin in other than autologous HCTs, the MASCC guidelines only recommend palifermin be used for patients undergoing autologous stem cell support preceded by TBI conditioning regimens until adequate evidence is available.<sup>9</sup> Additionally, the use of palifermin in pediatric patients has not been studied, and its safety and effectiveness has not been established.

Other growth factors and anti-inflammatory agents have also been investigated, with no clear evidence of benefit. Evidence regarding betamethasone and cytokines has been conflicting, and a single study of pentoxifyline, an inhibitor of proinflammatory cytokines, showed no effects.<sup>48-51</sup> A recently reported double blind placebo-controlled phase III trial showed that granulocyte-macrophage colony stimulation factor was effective in reducing radiation-induced OM.<sup>52</sup> Data regarding benzydamine, a non-steroidal anti-inflammatory drug used to prevent OM, are also conflicting. An initial study reported a 30% reduction in OM in patients with head and neck cancer receiving 50 Gy of radiation, but this effect disappeared at the more typical dose levels of 60 to 70 Gy.<sup>53</sup> It should be noted that benzydamine is not commercially available in the United States, but is readily available in Canada, Europe, South America, and Australia.

Amifostine is an organic thiophosphate that functions as a free radical scavenger and thus has been investigated as a radioprotectant. The FDA label for this drug states that it is intended to reduce the incidence of moderate to severe xerostomia in patients undergoing postoperative radiation treatment for head and neck cancer, when the radiation fields includes a substantial portion of the parotid glands. Amifostine is also approved for preventing nephrotoxicity associated with platinum compounds.<sup>54</sup> Nevertheless its use remains controversial in routine clinical practice. The Cochrane review notes 7 randomized studies of amifostine of variable quality in patients with head and neck cancer. It concluded that amifostine may prevent and reduce the severity of mucositis. A 2006 meta-analysis of amifostine came to somewhat different conclusions, reporting that amifostine significantly reduces the side effects of radiation therapy.<sup>55</sup> Amifostine has also been reported to reduce mucositis associated with high-dose melphalan in one prospective randomized trial and several retrospective studies.<sup>56-59</sup>

The MASCC guidelines do not provide specific recommendations for amifostine for OM, noting that “most of the studies ... have been small, single-center studies with conflicting results that do not help to delineate the role of amifostine in the reduction of mucositis.” The controversy surrounding amifostine is also related to associated side effects and to the idea that radiation-induced mucositis may be better addressed using improved radiation techniques, such as intensity-modulated radiation therapy (IMRT).

However, the available studies suggest that amifostine can significantly reduce xerostomia in patients undergoing radiation for head and neck cancer and can reduce mucositis associated with high-dose melphalan in patients undergoing autologous stem cell transplant. Currently institutional practices vary regarding the use of amifostine.

### Low-Level Laser Therapy

Although the exact mechanism of action is unclear, longstanding interest is focused on low level laser therapy (LLLT) as a preventive technique for OM. A preventive role for LLLT has been investigated in 2 settings: transplantation and radiotherapy for head and neck cancer. LLLT requires appropriate equipment but minimal training to apply. The 2006 MASCC guidelines note that LLLT is suggested in the transplantation setting. Since this review, additional randomized trials have been published, further supporting that role.<sup>60,61</sup> Antunes et al.<sup>60</sup> randomized 38 patients undergoing allogeneic or autologous stem cell support to a low-power laser therapy group or a standard care control group. In the laser group, 94.7% had OM of grade 2 or lower, compared with 31.5% in the control group. Additionally, when ulcers occurred, their size was significantly smaller in the laser group. In another larger randomized trial, Schubert et al.<sup>61</sup> compared 2 different low-level lasers (650 and 780 nm) and placebo in 70 patients undergoing HCT. The 650-nm wavelength reduced the severity of OM and pain scores. LLLT was well-tolerated, and no adverse events were noted. However, the authors also noted that further study is needed to truly establish the efficacy of LLLT and to define the optimal laser parameters, including optimal wavelength, energy density, and schedule.

The MASCC guidelines do not offer specific recommendations on LLLT in patients receiving radiotherapy alone for head and neck cancer. However, since publication of the guidelines, Arun Maiya et al.<sup>62</sup> reported on a study that randomized 50 patients with head and neck cancer to receive either LLLT or standard care. At the end of treatment, mean pain score and mucositis grade were significantly lower ( $P < .001$ ) in the study group compared with the control group.

This overview of preventive therapies illustrates the limited number of well-researched preventive options. Furthermore, studies have focused on grade 3 or 4 OM, with even more minimal research on mild to moderate OM, although the latter is a significant

clinical problem. For example, drugs that may be ineffective in preventing severe OM may be effective in preventing grade 2 OM; however, these studies have not been performed. Further research is vitally important, both on individual therapies and on combination or sequenced therapies.

### Management Strategies

Supportive care for OM currently centers on palliation. The most frequently recommended strategies focus on starting with bland rinses and topical anesthetics for established mild to moderately symptomatic OM. Normal saline (0.9%) rinses can often provide temporary relief of mild to moderate OM pain. Temperature of the solution (iced, room temperature, or slightly warmed) can be varied per patient desires. Patients are instructed to use several mouthfuls, swished, held, and expectorated as frequently as desired to provide comfort. It is also recommended that a bland rinse be used before application of other topical medications.

For many years, various different compounded mouthwashes with various ingredients, usually including topical anesthetics, have been recommended. These are collectively known as “magic mouthwashes,” and institutions often have their favorite formulation. The most common ingredients include diphenhydramine, viscous lidocaine, dyclonine magnesium hydroxide or aluminum hydroxide, nystatin, and occasionally corticosteroids.<sup>63</sup> Several studies have shown that for mild to moderate mucositis, bland saline rinses are as effective as these combination rinses and, obviously, much less expensive. Furthermore, nystatin has been shown to be ineffective in preventing oral candida colonization in a number of settings for immunocompromised patients.

Lidocaine products (viscous, gel, or solutions) can provide good topical anesthesia for OM discomfort and pain. Patients should be instructed to coat painful mucosal surfaces and then spit the solution out. Experts do not recommend patients generally gargle or swallow lidocaine for 2 reasons: 1) it can reduce the gag reflex and make the patient vulnerable to an aspiration pneumonia and 2) it will lead to systemic uptake and the safety of this has not been established. Inadequate data are available regarding maximum dose, but many physicians believe that 25 mL per day is within safe limits. Additionally, patients should avoid eating or performing oral hygiene measures

when their mouth is numb to avoid accidental trauma to oral tissues. Any agent that induces topical anesthesia without compromising mucosal health can be used, including diphenhydramine, benzocaine, and doxepin.<sup>64</sup>

A number of products were recently approved by the FDA as “devices” to manage OM symptoms, including Gelclair (Helsinn Healthcare SA, Lugano, Switzerland), Mugard (Access Pharmaceuticals, Dallas, TX), Mucotrol (Cura Pharmaceutical Co., Eatontown, NJ), and Caphosol (Cytogen, Princeton, NJ). However, these agents have not been sufficiently studied in well-designed clinical trials to support their recommendation. Other mucosal coating agents, such as Zilactin (Blair Laboratories, Columbus, IN) or Orabase (Colgate-Palmolive Company, New York, NY), although useful for occasional oral ulcers, probably have very limited usefulness in this setting.

Patient response to different oral care products, mouthwashes, and topical anesthetics is very individual and choice should be driven by patient preference. However, mouthwashes containing alcohol should be avoided because they can irritate damaged mucosal surfaces. Additionally, flavoring agents in oral care products (including toothpaste) and medications, especially mint and cinnamon, can cause pain. Efforts to find bland-flavored products can improve patient comfort and compliance.

The MASCC guidelines did not identify any specific recommended or suggested management options for OM. The guidelines did indicate that sucralfate should not be used for treatment of radiation-induced OM, and that chlorhexidine should not be used for chemotherapy-induced OM.

Notably, the MASCC guidelines only focused on treating mucositis and not on treating complicating infections. Prophylactic antivirals and antifungals are a consideration for patients receiving myelosuppressive regimens. Certain chemotherapeutic regimens with or without TBI may predispose patients to viral or fungal infection. In these situations, infectious disease protocols will usually recommend the use of prophylactic antiviral and antifungal agents. For example, bortezomib is associated with an increased risk of herpes simplex virus reactivation and acyclovir or valacyclovir would be indicated. Additionally, hematopoietic growth factors are indicated in patients with neutropenia along with prophylactic antibiotics to prevent infection.

## Principles of Management

### Communication

Preventing and managing OM require ongoing assessment and communication with the patient. Patterns of care are different for patients receiving radiation, standard-dose chemotherapy, or HCT. For example, patients receiving head and neck radiation therapy will typically be seen by a physician once or twice a week but by nursing staff 5 times a week. Conversely, patients receiving standard-dose chemotherapy will only see a physician at the beginning of a new cycle of therapy (once every 3–4 weeks). Patients will see nurses and other support staff more frequently.

Although oncologists should perform an oral examination on all patients to assess baseline risk for OM and provide ongoing monitoring, the nursing and support staff are best positioned to assess OM, determine the adequacy of supportive care, and provide ongoing patient education and encouragement to enhance patient compliance. Patients are familiar with many of the complications of chemotherapy, but many are not familiar with OM and its symptoms. Thus, patient education is important. In addition, patients may communicate different information to physicians and nursing or support staff, leading to discrepant assessments. In many cases, patients may be more forthcoming with nursing staff than physicians.

Patients should also be educated regarding the anticipated oral side effects of cancer therapies according to the risk assessment. For example, the patient with head and neck cancer who receives 70 Gy of radiation therapy over 7 weeks can expect OM to occur later in treatment, with a more prompt resolution, compared with the patient receiving radiation therapy twice a day with an additional boost of cisplatin chemotherapy. Additionally, pain may precede clinical evidence of OM, often beginning in the throat. Assessment of symptoms and functional impairment is extremely important.

Ongoing monitoring for an outpatient receiving chemotherapy requires attentive telephone triage to assess patient-reported outcomes, such as difficulty in eating and swallowing, that occur between clinic visits. As noted previously, the optimal topical anesthetics or mouthwashes are determined empirically for individual patients and may require multiple attempts. This type of ongoing assessment and feedback is necessary to direct supportive care, leading to a decrease in symptoms and a decreased risk of treatment delays and interruptions.

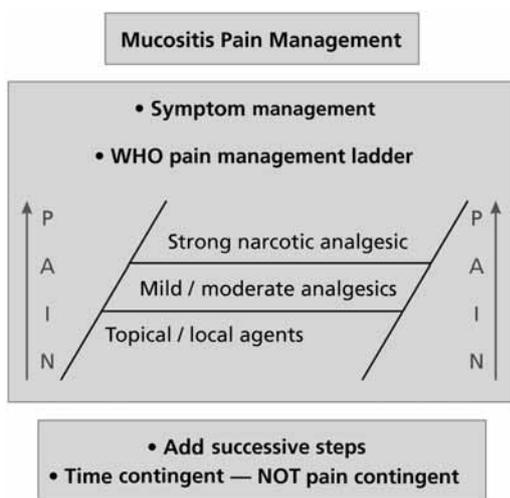
In the transplant setting, the predictable risk and time course of OM requires multidisciplinary involvement. Severe OM requiring hospital admission may be best managed by a pain management team.

### General Treatment Strategies

Although risk assessment and preventive strategies vary based on whether the patient is receiving chemotherapy, radiation therapy, or stem cell transplant, after OM is diagnosed, treatment strategies will generally proceed similarly. Treatment for painful OM (typically 3 on a 10-point scale) must be begun promptly so that the pain is controllable. An escalating stepwise therapy is recommended (Figure 2), in which additional therapy is sequentially added if symptoms are not adequately controlled.

Initial management of OM with mild pain levels consists of bland rinses. If this therapy is not adequate or pain is moderate, the next step in treatment is adding topical anesthetics. If topical agents are inadequate, the next step is the addition of systemic analgesics. Risk assessment and daily assessments can help anticipate how quickly a patient may need to move from one step to another. Patients at high risk for mucositis will predictably require early systemic analgesics. Thus, outpatients should be provided with appropriate prescriptions and instructions on how to obtain maximum analgesia. Additionally, patients who experienced mucositis in a previous cycle of chemotherapy will likely experience it in subsequent cycles.

A discussion of the numerous options for systemic analgesia, including the dose and route of delivery, is



**Figure 2** Step therapy for pain management in mucositis  
Courtesy of Mark Schubert, DDS, MSD.  
Abbreviation: WHO, World Health Organization.

beyond the scope of this discussion. However, basic principles of systemic pain management therapy for acute pain apply (Table 5).

Prophylactic treatment of constipation must be considered in any patient receiving narcotics. Fentanyl may be an appropriate choice for patients allergic to morphine and methadone. For this reason, caution is advised if fentanyl is used in opioid-naïve patients. Finally, meperidine is rarely used and is not recommended for patients receiving radiation therapy, especially those who need prolonged treatment.

Adequate step therapy for managing pain depends on ongoing patient feedback with consideration of alternative therapy if necessary. Physicians and support staff must not only frequently assess the effectiveness of pain management protocols, but also anticipate side effects of therapy with opioid prescriptions, follow up with the patient closely, and intervene if alternate or additional therapy is needed. Difficulty in swallowing oral tablets or capsules should be assessed; strategies to facilitate swallowing or changing to liquid formulations should be considered.

**Table 5 Routine Pain Management**

- Most convenient route of delivery: oral, patches, suppositories, intravenous
- Escalation of dose to effectiveness
- Avoid opioid-NSAID combinations when dosages need to be escalated
  - o NSAIDs will have dose limiting considerations
  - o Additionally, NSAIDs are contraindicated in myelosuppressed patients due to associated platelet dysfunction
  - o Simple analgesics, such as NSAIDs, are particularly effective to overcome tachyphylaxis to narcotics
- Patient should take pain medication on a "time-contingent basis" not on an "as needed" basis
  - o Consider time-release formulations or patches for ongoing pain management
  - o Patient-controlled analgesia has been particularly effective in managing severe oral mucositis in hospitalized patients. Patients can titrate pain medication levels to desired effectiveness as well as maintain a more steady state of analgesia and thus avoid the "pain roller coaster" effect noted with some opioid delivery methods
- Anticipate opioid side-effects and manage preemptively (e.g., constipation)

Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs.

A rapid increase in pain may indicate an otherwise clinically unapparent infectious process, such as *Candida* or herpes simplex virus in immunosuppressed patients. With appropriate treatment, pain levels should decrease with resolution of the infection. In addition to pain, patients with significant salivary gland dysfunction may have abundant thick mucus saliva secretions that can make it difficult to swallow. Excessive secretions may be a particular problem for patients receiving head and neck therapy, peaking at the third or fourth week. Secretions can be reduced with mucolytics drying agents. For example, antitussive syrups include antihistaminic agents that can be particularly helpful in secretion management. Scopolamine patches may also be effective. However, this approach can increase the patient's xerostomia complaints because of decreased lubrication of mucosal surfaces. Lorazepam may also be helpful to reduce the gag reflex and interrupt the vicious cycle of swallowing and gagging on pooled secretions.

### Specific Issues Related to Radiation Therapy

The key factors for mucositis risk associated with radiation therapy are target volume, location of tumor, fractionation scheme, and whether or not concurrent chemotherapy is used. Unlike OM from purely systemic therapies, radiation-related OM depends on the specific anatomy targeted. It may thus involve the oral cavity, oropharynx, nasopharynx, hypopharynx, cervical esophagus, and larynx. Radiation techniques can modify the risk of OM by limiting exposure to head and neck mucosal volumes. Specific shielding methods may be helpful, depending on the tumor location. IMRT or proton beam therapy may be used to limit exposure to the parotid glands, larynx, esophagus, and oral cavity. IMRT is now increasingly used for head and neck cancer, although the use of multiple beams with this technique makes it difficult to fully shield the anterior tongue and oral cavity as effectively as conventional radiation therapy with the limited number of beams. However, no consistent data suggests that IMRT for head and neck cancer is associated with a decreased risk of mucositis, although the mucositis itself may be less extensive because of the targeted radiation fields.<sup>65</sup>

All patients receiving head and neck cancer radiotherapy require more than a visual assessment of the

oral cavity, even edentulous patients. Timely referral to a dentist for oral and dental health assessment and correction of dental problems is critical. This includes management of caries, periodontal disease, endodontic infections, fractured teeth or defective restorations, and poorly fitting dentures. Guidelines for dental evaluation are readily available in the literature and included in all RTOG clinical trials protocols.

Counseling on adequate oral care is also important, including use of written patient education material and pain logs. Patient education can include dietary recommendations, such as avoiding breads and other starchy foods that are poorly digested because of radiation-induced salivary gland dysfunction. Lifestyle counseling can include cessation of smoking and reduction of alcohol intake, if appropriate.

Metal dental restorations or appliances can reflect and "back scatter" additional radiation into opposing soft tissues and thus can be associated with increased OM in adjacent areas. This radiation is of relatively lower energy, and strategies to hold soft tissues 5 to 10 mm away from metallic surfaces in the field of radiation can be very effective in preventing absorption of back-scattered radiation. Techniques range from gauze pads to athletic mouth guards to customized prosthetic mouth guards that absorb secondary electrons and increase the separation between the metal fillings and normal oral tissues. This can decrease radiation reaction in the adjacent areas.

Various devices can be used to position the tongue, and bite blocks can alter the level of separation of the jaws or cover a tooth during radiation therapy. In addition, simple customized devices can be made from various thermoplastic materials. All of these strategies can reduce the risk of OM, but they are frequently underused.

Placement of a prophylactic percutaneous endoscopic gastrostomy (PEG) tube may be considered in patients at high risk for OM and esophagitis. This can include patients presenting with significant dysphagia or weight loss, patients receiving platinum-based chemotherapy, or patients receiving radiation therapy to a large-volume tumor.<sup>66</sup> A prophylactic PEG tube can provide adequate hydration, thus avoiding treatment interruptions. In addition, a PEG tube is easier to place when the patient is relatively healthy than when the patient has severe OM and esophagitis, which can make managing the airway difficult. Prophylactic placement of PEG tubes may

be controversial; risks of placement are not negligible, and with adequate supportive care, many patients may not need one. Additionally, patients with prophylactic PEG tubes may have a longer period of dependency, although this has not been evaluated in formal studies.

## Future Directions

### Targeted Therapy

Understanding of the pathogenesis of mucositis has improved over the past 15 years and has, in turn, fueled research on prevention and therapeutic strategies. The original concept of OM was simplistic—a direct effect of chemotherapy and radiation therapy on the basal layer epithelium leading to atrophy, breakdown, and ulceration of the epithelium. However, the varying response of OM to different treatment modalities suggested a more complex process, and research began to focus on the maze of subclinical cellular pathways. In 1998, Sonis<sup>7</sup> proposed a model of mucositis that has been updated continuously as additional research is reported. The following 5 steps describe the pathobiology of mucosal injury and eventually healing:

**Initiation:** Chemotherapy and radiation produce reactive oxygen species (ROS) within cells that lead to direct damage to cells, supporting tissues, and vasculature. ROS production then serves to initiate a number of responses throughout mucosal epithelial and subepithelial tissues.

**Upregulation and Message Generation:** ROS results in the upregulation of nuclear factor- $\kappa\beta$ , which ultimately results in the generation of inflammatory cytokines, activation of the ceramide and Cox2 pathways, and production of matrix metalloproteinases. These steps lead to inflammation, angiogenesis, apoptosis, and widespread tissue injury. Mucotoxicity varies among chemotherapies and dosing regimens because of the pattern and array of injury.

**Signaling and Amplification:** In this stage, tumor-necrosis-factor-alpha produced during the previous step can re-upregulate nuclear factor- $\kappa\beta$ , leading to a subsequent round of inflammatory cytokine production and activation of the COX-2 and ceramide pathways. This, in turn, results in a second wave of tissue damage throughout the epithelial and submucosal tissues.

**Ulceration:** If epithelial damage is severe enough, frank ulceration occurs. The exposure of inflammatory

cells and macrophages to the invading bacteria leads to the release of inflammatory cytokines (IL-1, IL-6, and tumor necrosis factor- $\alpha$ ), which not only leads to additional inflammation and tissue damage, but also furthers upregulation of nuclear factor- $\kappa\beta$  and ultimate production of more inflammatory cytokines. All of these processes not only cause significant pain, but potentially result in local infection and bacteremia and/or sepsis in immunosuppressed patients.

**Healing:** As the waves of inflammation and tissue damage begin to subside, the epithelial tissues provide signals to the extracellular matrix, prompting healing of the areas of ulceration with restoration of normal mucosal thickness. However, a number of changes can persist, including angiogenesis, damaged fibroblasts, and alterations in how the mucosal maintains itself.

At each phase, a complex series of events occur, often driven by specific genetic factors, which result in the production of cytokines that can not only directly damage tissues but act further as initiators and amplifiers of the various previously stimulated pathways. A detailed discussion of the unfolding cellular pathways is beyond the scope of this discussion, but understanding the specific cellular pathways is the precursor to developing preventive and treatment strategies targeted to them. This type of research also creates the potential for targeting specific pathways and sequencing therapies based on the different stages of mucositis. Therapies under investigation include tumor necrosis factor inhibitors, cox-2 inhibitors, free radical scavengers, and growth factors.

Oncologists are familiar with individual patient variability in the incidence of mucositis associated with a given treatment regimen. This may reflect the role of genetically based risk factors, particularly in the incidence of mild to moderate mucositis or in its duration. As treatment intensity increases, the ability of genetic factors to modulate mucositis incidence will disappear.

Pharmacogenetics is an active area of research. As was noted, metabolism and thus the effect of methotrexate is mediated by the *MTHFR* gene, which has 3 polymorphisms, CC, CT, and TT. In a study of 220 patients with chronic myelogenous leukemia receiving methotrexate as a component of GVHD prophylaxis, Ulrich et al.<sup>6</sup> found that the TT polymorphism was associated with a significantly higher incidence of OM than other polymorphisms.

## Prevention and Management of Mucositis

**Table 6 NCCN Task Force Recommendations for the Prevention and Management of Mucositis in Cancer Care****Risk Factors and Assessment of OM**

- The use of a valid and reliable scale is recommended for the routine clinical assessment of OM.
- Regular assessment of OM by all members of the oncology team will facilitate standard interventions for specified events. This is similar in concept to measuring body temperature or blood pressure.
- Because of the small number of clinical trials on the prevention and management of OM, recommendations are based on a combination of evidence-based information and expert judgment.
- Assessment of treatment-related OM risk factors should be performed so that clinicians can anticipate and promptly treat OM, thus allowing the goals of no dose reductions or delays.
- Patients receiving specific drugs or combinations known to be associated with a high-risk for OM, patients receiving HCT, and patients receiving accelerated radiation or combined modalities should receive special care, including frequent oral assessments.
- A dental examination is recommended for all patients to identify and treat potential sources of infection and areas at risk for exacerbating OM.
- All patients scheduled for high-dose therapy and HCT should undergo formal dental evaluation by a dentist familiar with OM risk factors.
- Patients should be encouraged to modify behavior to reduce the incidence and severity of oral mucosal trauma, including avoiding rough textured foods, vigorous or excessive chewing, and oral habits that can injure compromised mucosal surfaces (lip or cheek chewing).

**Prevention Strategies**

- Good oral hygiene is a universally recommended “good clinical practice.”
- Cryotherapy is recommended in patients receiving bolus-dosed 5-FU or edatrexate therapy or high-dose melphalan before HCT.
- Bland oral rinses are commonly used as a supportive care measure. Clinical trials have not definitively shown superiority of one rinse over another, and therefore the choice should be driven by clinical assessment and patient preference. These rinses provide mild symptomatic relief, moisturize tissues, and remove debris.
- Topical oral antimicrobials (rinses or lozenges) should not be used to prevent OM. They can, however, have value in reducing microbial colonization (e.g., bacterial dental plaque) when routine oral hygiene is not possible.
- Palifermin is recommended as a preventive therapy in patients receiving TBI-containing conditioning regimens before autologous stem cell transplantation.
- Because of the preliminary nature of the data, palifermin is not routinely recommended in other settings, including autologous transplant without TBI, allogeneic transplant, or other malignancies.
- Amifostine is recommended for the prevention of xerostomia related to head and neck irradiation and can reduce mucositis associated with high-dose melphalan.

**Treatment Strategies**

- Bland rinses can be used for mild to moderate OM pain on an as needed basis.
- Topical anesthetics can be used to provide OM pain relief. Patients should take care to avoid mucosal injury while tissues are anesthetized, and they should not gargle or swallow the solution unless instructed. With more severe mucositis pain, topical anesthetics can be used for “breakthrough pain” until analgesics can be administered and become effective.
- The formulation of mouthwashes containing topical anesthetics (“magic mouthwashes”) varies among institutions. No one formulation has been shown to be superior; selection should be driven by patient preference. Alcohol-containing mouthwashes should be avoided. Overall patient acceptance of these rinses should be assessed regularly and adjustments to the formulation or alternative preparations should be made if the rinse is either unacceptable or ineffective.
- Prophylactic antiviral and antifungal therapy may be considered in myelosuppressive therapy to prevent infections that can aggravate OM.

**General Management Strategies**

- Adequate patient education and communication between the patient and all members of the cancer care team are critical, particularly since nursing staff and other support staff typically interact with the patient more frequently than the physician. Nurses are often the first to become aware of symptoms or clinical evidence of OM.
- Patients should be educated on the typical time course and duration of anticipated mucositis based on treatment related risk factors.
- In the transplant setting, management of mucositis requires multidisciplinary involvement.

**Table 6 Continued**

- A stepwise approach to mucositis management is recommended, starting with bland rinses, then topical anesthetics, then systemic analgesics of increasing strength as needed.
- Patients must be closely questioned regarding the effectiveness of therapy and side effects, with prompt intervention for inadequate pain relief.
- Different strategies are needed during different periods of mucositis. Supportive care medications must be adjusted at time intervals tailored to emerging symptoms.

**Radiation Therapy Management Strategies**

- In patients with metal dental restorations undergoing radiation therapy, use of a dental guard, bite block, cotton roll, wax around the filling, or other devices to separate the metal from the mucosa will reduce adjacent mucositis.
- Placement of a prophylactic PEG tube may be considered in patients at high risk for mucositis and esophagitis, typically patients with a large volume of tumor who are receiving radiation therapy and platinum-based chemotherapy, or patients presenting with significant dysphagia or weight loss.

Abbreviations: HCT, hematopoietic cell transplant; OM, oral mucositis; PEG, percutaneous endoscopic gastrostomy; TBI, total body irradiation.

The pharmacogenetics of 5-FU is another research interest.<sup>67</sup> For example, the lack of enzymes to efficiently metabolize 5-FU may be simultaneously associated with an increased risk for mucositis and an increased anti-cancer effect. Keen research interest has also been seen in microarray analysis to reveal genetic influences on inflammation and mucosal repair, contributing to the variability in risk among individuals.<sup>68,69</sup>

**Preventive Therapies**

Palifermin is now under investigation for prevention of treatment-related OM in cancers requiring multicycle therapy. One of the key issues in this setting is the prolonged exposure to palifermin inherent in multicycle regimens. The long-term effect on the underlying cancer is unknown as are possible long-term adverse events. Therefore, results of promising preliminary studies must be viewed with caution. For example, Rosen et al.<sup>70</sup> studied palifermin in a placebo-controlled randomized trial of 64 patients with colorectal cancer receiving 5-FU and leucovorin. The treatment group received 40 mcg/kg for 3 consecutive days before each of 2 consecutive cycles of chemotherapy. The incidences of grade 2 or higher OM in the treatment group in the first and second cycles were 29% and 11% compared with 61% and 47%, respectively, in the placebo group. Almost one third of the patients in the placebo group required some form of dose reduction, compared with only 14% of the treatment group. Numerous other studies of a variety of solid tumors or hematologic malignancies in non-transplant settings are currently underway.

Palifermin is also being investigated in patients with head and neck cancer treated with chemoradiation in both the United States and Europe. RTOG 0435 is a current phase III double-blind study of patients with advanced head and neck cancer undergoing chemoradiation. Until these trials are completed, outside of the autologous transplant setting, palifermin should only be used in the context of a formal mucositis intervention trial.

Velafermin is a recombinant human fibroblast growth factor being investigated for the prevention of chemotherapy-induced OM. Preliminary results of a phase II randomized study of patients receiving high dose chemotherapy with or without TBI were presented in 2006.<sup>71</sup> Patients were randomly assigned to receive either placebo or 1 of 3 doses of velafermin delivered with a single intravenous infusion 24 to 36 hours after stem cell transplantation. Results suggested velafermin was associated with a reduction in the incidence and duration of grade 3 to 4 OM. Although benefits were seen, the study failed to meet the established endpoints, and further studies have been suspended.

RK-0202, a preparation of the antioxidant N-acetylcysteine delivered as an oral rinse, has been investigated as a technique to reduce the incidence of OM in patients undergoing radiation therapy for head and neck cancer. Preliminary results of a phase II randomized, placebo-controlled trial were presented in 2006. In this study, 110 patients receiving a cumulative radiation therapy dose of 60 Gy received either 2 different concentrations of RK-0202 or placebo just before radiation therapy and 6 times daily throughout

## Prevention and Management of Mucositis

radiation therapy.<sup>72</sup> Compared with the placebo group, patients receiving the higher 10% RK-0202 formulation showed significant reductions in the incidence of severe OM and reduced need for feeding tubes and opiate analgesia. No adverse effects were seen. Further studies are planned in patients receiving chemoradiation.

### Communication Strategies

As noted previously, ongoing patient assessment and monitoring is a key component of mucositis management. In the future, Web-based programs will probably be used to facilitate multidisciplinary communication. For example, patient self assessments, completed at home or in the oncology office, can be transmitted directly to nursing or other support staff. These programs can be equipped with alarms to detect nonadherence or to trigger proactive communication between the oncology staff and patient.

### Summary

OM is associated with significant morbidity that can lead to treatment delays and interruptions and the use of significant health care resources. However, definitive data on prevention and treatment of OM is relatively scarce, and management of OM must be driven in part by expert and empiric judgment. Using the clinical practice guidelines from the MASCC as a baseline for discussion, the NCCN Task Force on Prevention and Management of Mucositis in Cancer Care reviewed additional published data integrated with expert opinion to produce a comprehensive approach to the management of mucositis. The Task Force recommendations are summarized in Table 6.

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## Prevention and Management of Mucositis

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Post-test

Please circle the correct answer on the enclosed answer sheet.

1. Which of the following outcomes are related to mucositis?
  - a. Dysphagia
  - b. Bleeding
  - c. Fatigue
  - d. Electrolyte imbalance
  - e. All of the above
2. Which of the following is/are TRUE?
  - a. Dose reductions in radiation therapy are frequently related to mucositis.
  - b. Hospitalization related to the side effects of radiation therapy are most commonly caused by skin breakdown and related infection.
  - c. Mucositis is a frequent cause of chemotherapy dose reductions.
  - d. All of the above
3. Which statement(s) correctly interpret(s) the WHO oral mucositis scale?
  - a. Grade 0 describes mild erythema.
  - b. Grade 2 describes the appearance of shallow ulcers.
  - c. Grade 3 describes the presence of oral ulcers and the ability to eat solid foods.
  - d. Grade 4 describes the inability to tolerate oral alimentation.
  - e. All of the above
4. Which is/are TRUE regarding the use of a reproducible mucositis grading scale?
  - a. The lack of a consistently used scale hampers data comparison across studies and therapeutic modalities.
  - b. The currently used scales all have a consistent definition of different clinical levels of mucositis.
  - c. Consistent use of mucositis scales in clinical practice allow interventions to be triggered at specific events or cut-off points.
  - d. All of the above.
  - e. Only a and c
5. Different chemotherapy regimens are classified according to *emetogenic* potential. Why is categorizing regimens according to their *mucositis* potential difficult?
  - a. Patient factors, such as age and comorbidities, also affect risk of developing mucositis.
  - b. Many variables associated with chemotherapy regimens may be related to mucositis risk, such as individual drugs, combination therapy, and dose scheduling.
  - c. A drug may not be associated with a significant risk when used as monotherapy, but the risk may markedly increase when the same drug is used in combination.
  - d. All of the above
6. What are the limitations of the current literature regarding mucositis?
  - a. Meta-analyses focusing on randomized studies have addressed both preventive and treatment strategies for mucositis. However, mucositis is an emerging area of research with a relative paucity of randomized studies, and meta-analysis is not the optimal approach to assessing the literature.
  - b. Mucositis endpoints have not been routinely incorporated into clinical trials of new drug therapies or radiation therapy.
  - c. Although guidelines exist regarding individual treatment options and therapies, a comprehensive approach combining risk assessment and pharmacologic and nonpharmacologic therapies is needed.
  - d. All of the above
  - e. None of the above
7. Which of the following is/are TRUE regarding chemotherapy-related oral mucositis risk?
  - a. Mucositis in a previous cycle of chemotherapy is poorly predictive of mucositis in a subsequent cycle because of intervening patient factors
  - b. Cycles of myelosuppressive chemotherapy do not have a cumulative effect.
  - c. In the stem cell transplant setting, mucositis risk is related to the conditioning regimen used.
  - e. All of the above
  - f. Only a and b
8. Which of the following best describes the timing of oral mucositis related to radiation therapy of head and neck cancer?
  - a. Mucositis typically occurs as a delayed reaction, occurring up to a month after therapy is completed.
  - b. Mucositis peaks in the first 2 weeks of therapy, with slow resolution over the next several months.
  - c. Mucositis peaks at 5 to 6 weeks, with resolution during weeks 8 to 12.
  - d. The time course of mucositis is highly unpredictable in head and neck cancer because of patient factors.
9. Which of the following is/are TRUE regarding patient-related risk factors for oral mucositis?
  - a. Consistent data show that the risk of oral mucositis increases with age.
  - b. Women appear to be at higher risk for chemotherapy-associated mucositis compared with men.
10. Which of the following is/are TRUE regarding mucositis risk?
  - a. Mucositis risk is higher in patients with a history of mucositis.
  - b. Mucositis risk is higher in patients with a history of mucositis.
  - c. Mucositis risk is higher in patients with a history of mucositis.
  - d. Mucositis risk is higher in patients with a history of mucositis.
  - e. None of the above; chemotherapy regimens have been accurately categorized according to mucositis risk.

- c. Consistent data show that nutritional status is independently associated with mucositis risk.  
 d. Various studies have reported that xerostomia is associated with an increased risk of mucositis.  
 e. Only a and c  
 f. Only b and d
10. Which of the following is/are TRUE regarding treatment strategies for oral mucositis?  
 a. Supportive care typically involves the use of a variety of different mouthwashes.  
 b. No one mouthwash has been shown to be superior to another.  
 c. Choice of mouthwash should be driven by clinical assessment and patient preference.  
 d. All of the above  
 e. None of the above; mouthwashes containing alcohol have been shown to be superior.
11. Which of the following is/are TRUE regarding ongoing assessment of mucositis?  
 a. Communication between the patient and nursing or other support staff is critical.  
 b. An oral assessment by physicians and nurses should be integrated into the ongoing care of patients.  
 c. Patient education is critical; some patients can be trained to do oral assessments in the home.  
 d. All of the above
12. Which of the following is/are TRUE regarding step therapy for the treatment of mucositis?  
 a. Step therapy focuses on the symptomatic treatment of pain associated with mucositis; treatment is initiated with topical and local agents, with additional therapies added depending on the degree of pain.  
 b. The use of strong narcotic analgesics should be withheld until the patient experiences severe pain.
- c. Oral mucositis is typically associated with mucositis throughout the gastrointestinal track; therefore, when mucositis is severe, systemic treatment is needed to treat a systemic disease.  
 d. Treatment response can be assessed at weekly intervals.  
 e. All of the above  
 f. Only a and b
13. Which of the following is/are TRUE regarding the management of patients receiving radiation therapy for head and neck cancer?  
 a. Because metal dental fillings cannot absorb and scatter radiation, oral mucosa within 3 mm of a metal filling is not at higher risk of mucositis.  
 b. During radiation, any kind of dental guard, cotton roll, or wax that separates the filling from the adjacent mucosa can be protective.  
 c. Devices to position the tongue out of the radiation field and bite blocks to position the jaws are overused.  
 d. Simple mouth guards cannot protect the teeth.  
 e. All of the above  
 f. None of the above
14. Which of the following is/are TRUE of ongoing research regarding mucositis prevention and treatment?  
 a. Growing understanding of the underlying cellular pathways leading to mucositis creates the possibility of targeted therapies.  
 b. Emerging genetic factors may also refine patient-related mucositis prognostic factors.  
 c. Innovations in communications strategies, such as web-based programs, may assist in the critical ongoing assessment of mucositis over the course of therapy.  
 d. All of the above  
 e. Only a and b

### Post-Test Answer Sheet

Please circle one answer per question. A score of at least 70% on the post-test is required.

- |    |   |   |   |   |   |     |   |   |   |   |   |   |
|----|---|---|---|---|---|-----|---|---|---|---|---|---|
| 1. | a | b | c | d | e | 8.  | a | b | c | d | e | f |
| 2. | a | b | c | d | e | 9.  | a | b | c | d | e | f |
| 3. | a | b | c | d | e | 10. | a | b | c | d | e |   |
| 4. | a | b | c | d | e | 11. | a | b | c | d |   |   |
| 5. | a | b | c | d | e | 12. | a | b | c | d | e | f |
| 6. | a | b | c | d | e | 13. | a | b | c | d | e | f |
| 7. | a | b | c | d | e | 14. | a | b | c | d | e |   |

<p><b>Please evaluate the achievement of the learning objectives using a scale of 1 to 5.</b> (1 = Not met; 3 = Partially met; 5 = Completely met)</p> <p>Describe the pathophysiology, clinical manifestations, prevention, and treatment of oropharyngeal mucositis. 1      2      3      4      5</p> <p>Discuss the early recognition and assessment of oropharyngeal mucositis. 1      2      3      4      5</p> <p>Identify pharmacologic and non-pharmacologic interventions that can help prevent or mitigate the condition's negative impact on the patient's ability to receive and continue therapy. 1      2      3      4      5</p> <p>Summarize the scientific evidence underlying the management, including a stage-based approach, of oropharyngeal mucositis secondary to cancer therapy. 1      2      3      4      5</p>	<p><b>Please indicate the extent to which you agree or disagree with the following statements:</b> (1 = Strongly disagree; 3 = Not sure; 5 = Strongly agree)</p> <p>The material was presented in a fair and balanced manner. 1      2      3      4      5</p> <p>The information presented in this monograph was pertinent to my educational needs. 1      2      3      4      5</p> <p>The information presented was scientifically rigorous and up-to-date. 1      2      3      4      5</p> <p>The information presented in this monograph has motivated me to modify my practice. 1      2      3      4      5</p> <p>I would recommend this monograph to my colleagues. 1      2      3      4      5</p>
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**NCCN Task Force Report: Prevention and Management of Mucositis in Cancer Care**

Release Date: January 30, 2008  
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