Mucositis, or damage to the mucosal surfaces of the body that develops after chemotherapy, radiotherapy, or even targeted anticancer therapy, was originally described as a simple inflammatory condition and was thought to be limited to the mouth. It is now clear that both of these concepts were incorrect.
The pathogenesis of mucositis is quite complex, and mucositis can affect the entire gastrointestinal (GI) tract. In fact, it probably also affects other mucosal surfaces, such as those of the nasal passages, eyes, and genitourinary and respiratory tracts.2,5,6

**Mucositis: Symptoms, Measurement, Risk Factors, and Burden**

The symptoms of mucositis vary according to the area of mucosa affected. Radiation-induced mucositis is largely limited to tissues within the radiation field, although the peripheral mucosa may also be affected. Additionally, its indirect effects may result in systemic symptoms, such as fatigue, malnutrition, and nausea.5,7 In contrast, chemotherapy-induced mucositis may occur throughout the GI tract. Oral mucositis (OM) is characterized by mouth pain and ulceration2,8; symptoms of esophageal mucositis (esophagitis) include retrosternal chest pain and odynophagia.5,9,10 Mucositis of the small intestine manifests with abdominal pain, bloating, and diarrhea,4,5,11 and mucositis of the distal bowel leads to pain on defecation and bloody mucus in the stool.2,5 Importantly, mucositis may lead to local and systemic infections and death (Figure 1).2,5

OM is probably the best-studied form of the condition, and numerous measurement scales have been devised to describe its severity. Fewer scales exist for mucositis in more distal regions. Scales serve several purposes: assessing toxicity, obtaining data for research, enabling communication between professionals, and functioning as nursing management tools. The toxicity scales that are most widely used include the World Health Organization (WHO) Oral Mucositis Assessment Scale and the National Cancer Institute Common Toxicity Criteria (NCI-CTC). For OM, the WHO Scale (Figure 2) is the most commonly used and probably the easiest tool to apply, whereas for mucositis in other parts of the GI tract, the NCI-CTC are easy to use and reproducible. Essentially, the most appropriate scale is based on a 5-point system, on which a grade of 0 indicates the absence of mucositis and grades of 1 through 4 indicate mild, moderate, severe, and life-threatening mucositis.

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**Figure 1. Clinical effects of mucositis.**
The traditional risk factors for mucositis are patient- and treatment-related rather than specifically associated with a particular cancerous disorder. However, these general risk factors are imprecise, and improved methods to assess risk are needed. Patient-related factors include age (mucositis is less likely to develop in pediatric patients undergoing bone marrow transplantation [BMT] than in adults) and body mass (mucositis is more likely to occur in patients with a larger body mass). Treatment-related factors depend on the regimen and dose used and on whether radiotherapy and chemotherapy are used alone or in combination (Table 1).

In addition to causing incredible pain and discomfort, mucositis is associated with a series of adverse health and economic outcomes. The pain of mucositis often necessitates the use of opioid analgesics. In patients who become leukopenic from myeloablative chemotherapy, the ulcerations associated with mucositis frequently serve as sites for secondary infection and systemic portals for pathogenic bacteria. Mucositis-induced impairment of oral function is a frequent cause of weight loss and the requirement for parenteral feeding.

Epidemiology and Pathobiology

Like many toxicities of cancer therapy, mucositis has been historically underreported. Consequently, its true incidence is hazy. It is certain that patients being treated with radiation or chemoradiation for cancers of the head and neck are at high risk for OM (>50%; Table 2). Similarly, patients receiving radiation for the treatment of lung or prostate cancers are very likely to develop esophagitis or proctitis, respectively. Conditioning regimens before hematopoietic stem cell transplant (HSCT), especially those that include total-body irradiation or high-dose melphalan (Alkeran, Celgene) are generally highly likely to cause mucositis. The incidence of mucositis among patients being treated for non–head and neck solid tumors is less clear. Regimens containing 5-fluorouracil (5-FU) have always been thought to cause mucosal damage. Diarrhea and OM in these patients seem to be more common than in patients being treated with radiation or chemoradiation for cancers of the head and neck.

The pathogenesis of mucositis is more complex than was originally believed. Mucositis is no longer thought to result only from direct injury to epithelial stem cells. It is now understood that the clinical phenotype(s) that characterize mucositis is the cumulative result of direct cell death critically coupled with stem cell damage that is mediated by a variety of signaling pathways. These originate in the cells and tissues of the lamina propria, which include endothelial cells, fibroblasts, and a range of inflammatory cells.

Data on the OM and the more distal GI mucositis resulting from targeted therapies is less clear than that on non–head and neck solid tumors. Many of the targeted agents developed to date are highly likely to cause mucosal toxicity. The incidence and nature of mucositis associated with targeted therapies continues to be determined from continuing reporting of regimen-related toxicities and a retrospective evaluation of the Multinational Association of Supportive Care in Cancer (MASCC) retrospective evaluation of patients undergoing bone marrow transplantation (BMT) and hematopoietic stem cell transplant (HSCT).

The World Health Organization (WHO) Oral Mucositis Assessment Scale.

Figure 2. World Health Organization Oral Mucositis Assessment Scale.
cells (although mucositis is not a classic inflammatory reaction). It is also probable that the extracellular matrix (ECM) plays a role in the course of the condition.\textsuperscript{2,8,16}

The development and resolution of radiation- or chemotherapy-induced mucositis are associated with a series of identifiable, interactive biological events, the definition of which continues to evolve. Importantly, their recognition has provided potential targets for innovative interventional strategies.

The administration of chemotherapy or radiation results almost immediately in the generation of oxygen free radicals.\textsuperscript{2,8,16} The damaging effects of reactive oxygen species (ROS) on cells and their DNA are well described. ROS, along with chemotherapeutic agents and radiation, are capable of activating a wide range of signaling pathways that may lead to cellular injury or apoptosis. Among these are transcription factors, such as nuclear factor-\textkappa B and Akt, and enzymes, such as sphingomyelinase, ceramide synthases, and matrix metalloproteinases. ROS may also cause the local destruction of connective tissue elements. In each of these cases, a sequence of activities occurs that culminates in cellular death. Furthermore, many of the proteins that are generated, such as the proinflammatory cytokines, influence and amplify the local tissue response and the resultant tissue injury. The cumulative effects of these mechanisms on the epithelium lead to the cessation of replication, and atrophy is followed by ulceration.

Ulceration is the clinical entity most frequently associated with mucositis, yet it represents only a part of the mucositis continuum. Secondary bacterial colonization of ulcerative lesions is typical. Both Gram-positive and Gram-negative organisms produce cell wall products that in themselves stimulate connective macrophages to release additional damaging cytokines. Over time,

<table>
<thead>
<tr>
<th>Table 1. Risk for Oral Mucositis by Conditioning Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies, No.</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>TBI</td>
</tr>
<tr>
<td>Busulfan (no TBI)</td>
</tr>
<tr>
<td>Other (no TBI)</td>
</tr>
<tr>
<td>Stem cells: myeloma</td>
</tr>
<tr>
<td>Stem cells: solid</td>
</tr>
<tr>
<td>TBI</td>
</tr>
<tr>
<td>Busulfan-cytarabine-etoposide (no TBI)</td>
</tr>
<tr>
<td>Melphalan-carboplatin-etoposide (no TBI)</td>
</tr>
</tbody>
</table>

OM, oral mucositis; TBI, total-body irradiation
Based on reference 2.
Treatment

MASCC’s recently published “Updated Clinical Practice Guidelines for the Management of Mucositis” offer limited therapeutic recommendations (Table 3), but they show advances in the field since the initial guidelines were published in 2004. Intravenous palifermin (Kepivance, Amgen) is the only drug FDA approved for the treatment of mucositis, although its indication is limited to decreasing the incidence and duration of severe OM in the BMT setting. There are, however, other FDA-approved palliative agents (Caphosol, Cytoppen) that have proved effective in the management of OM. Cost is also a consideration when choosing a therapy, as palifermin can be more expensive. To date, there have been no head-to-head trials comparing the efficacy of palifermin with palliative agents.

Palifermin, which is an N-truncated recombinant human keratinocyte growth factor-1 (a member of the fibroblast growth factor [FGF] family), should be considered in patients undergoing HSCT. In a randomized, double-blind Phase III trial, 212 patients with hematologic cancers received palifermin (60 mcg/kg per day) or i.V. placebo for 3 days immediately before the initiation of conditioning therapy and for 3 days posttransplant. Compared with placebo, palifermin was associated with significant reductions in the incidence of grade 4 OM (20% vs 62%; P<0.001). Palifermin reduced the duration of severe OM from 10.4 days (in the placebo group) to 3.7 days and was associated with a 61% reduction in parenteral opioid use. Also noted were a reduction in the use of total parenteral nutrition and improvements in eating, talking, sleeping, swallowing, and drinking.

A large number of compounds are in the development pipeline. Among these are valifermin (Curagen Corporation), another member of the FGF superclass (the same class as palifermin), which is being evaluated in a Phase II trial in HSCT recipients. Alizyme, a British company, is investigating the efficacy of a plant lectin in the treatment of mucositis. N-acetyl cysteine in a proprietary formulation (Pro-gelz, Endo Pharmaceuticals) recently was reported to delay the onset of radiation-induced mucositis in patients with head and neck cancer. Its efficacy may be related to its ability to attenuate free radicals and biological mediators. L-Glutamine in a proprietary oral suspension (Saforis, MGI Pharma) was effective in reducing the incidence of ulcerative mucositis in patients receiving chemotherapy for breast cancer. A number of other compounds are in early-stage clinical studies or in preclinical development.

Palliation has been the historic approach for mucositis. Magic mouthwash, usually locally formulated and often based on institutional folklore, is part of many hospital formularies. Most are variations on a theme of a topical analgesic (lidocaine or benadryl) and a delivery agent (Maalox or Kaopectate). Despite their popularity, there is a great deal of evidence to suggest that their efficacy is about the same as that of saline. Although clearly not ideal, until active, mechanistically based compounds successfully make their way through the approval process, palliative agents may provide some symptomatic relief for suffering patients. Virtually all of these have been classified as devices; hence, the approval process is decidedly less rigorous than that for pharmaceuticals or biologics. Among the palliative agents are Mucotrol, MuGard, and Gelclair, all of which are topically applied to form a barrier over ulcerated mucosa in an attempt

Table 2. Risk for and Health Burden Of Oral and GI Mucositis

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Risk for Mucositis</th>
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</thead>
<tbody>
<tr>
<td>Myelosuppressive chemotherapy</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>Standard-dose chemotherapy</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Chemoradiotherapy</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>Head and neck radiotherapy</td>
<td>&gt;50%</td>
</tr>
</tbody>
</table>

Grade 3/4 Oral or GI Mucositis Is Associated With:

- 3-fold increase in risk for chemotherapy dose reduction
- 3-fold increase in risk for infection and infection-related death during myelosuppression
- 10-fold increase in use of TPN and fluids
- 10-fold increase in use of opioid analgesics
- 2-fold increase in ER visits
- additional 7 days of hospitalization per episode
- incremental cost of >$3,500 per episode

ER, emergency room; GI, gastrointestinal; TPN, total parenteral nutrition

Based on reference 2.

signals from the ECM result in the migration, proliferation, and differentiation of the bordering epithelium to fill in the ulcerated area.

Although the preceding description need not simplify the biological processes leading to the development of mucositis, it nevertheless provides an insight into the complexity of the condition. As new potential treatments are studied, it is becoming clearer that agents with mechanistic pleotropism are among the most effective.
Table 3. Summary of Changes to the Evidence-Based Clinical Practice Guidelines for Care of Patients With Oral and Gastrointestinal Mucositis

<table>
<thead>
<tr>
<th>Oral Mucositis</th>
<th>Foundation of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous Guideline</strong></td>
<td>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 therapies. 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.</td>
</tr>
<tr>
<td><strong>Updated or New Guideline</strong></td>
<td>The panel recommends patient-controlled analgesia with morphine as the treatment of choice for OM pain in patients undergoing HSCT. Regular oral pain assessment with validated instruments for self-reporting is essential.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiation Therapy—Prevention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>The panel recommends that sucralfate not be used for the prevention of radiation-induced OM.</td>
</tr>
<tr>
<td>None</td>
<td>The panel recommends that antimicrobial lozenges not be used for the prevention of radiation-induced OM.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High-Dose Chemotherapy With or Without Total Body Irradiation Plus Hematopoietic Stem Cell Transplantation—Prevention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>In patients with hematologic malignancies receiving high-dose chemotherapy and total-body irradiation with autologous stem cell transplant, the panel recommends the use of keratinocyte growth factor-1 (palifermin) in a dose of 60 mcg/kg per day for 3 days before the conditioning treatment and for 3 days post-transplant for the prevention of OM.</td>
</tr>
<tr>
<td>None</td>
<td>The panel suggests the use of cryotherapy to prevent OM in patients receiving high-dose melphalan.</td>
</tr>
<tr>
<td>None</td>
<td>The panel suggests that granulocyte–macrophage colony-stimulating factor mouthwashes not be used for the prevention of OM in patients undergoing HSCT.</td>
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</table>

<table>
<thead>
<tr>
<th>Gastrointestinal Mucositis</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Basic Bowel Care and Good Clinical Practices</td>
<td>The panel suggests that basic bowel care include the maintenance of adequate hydration, and that consideration be given to the potential for transient lactose intolerance and the presence of bacterial pathogens.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Radiation Therapy—Prevention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>It is suggested that amifostine (Ethyol, MedImmune) in a dose of at least 340 mg/m² may prevent radiation proctitis in those receiving standard-dose radiation therapy for rectal cancer</td>
</tr>
</tbody>
</table>

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<tr>
<th>Standard- or High-Dose Chemotherapy—Prevention</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>The panel recommends that systemic glutamine not be used for the prevention of gastrointestinal mucositis.</td>
</tr>
</tbody>
</table>

**HSCT**, hematopoietic stem cell transplantation; **OM**, oral mucositis


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to protect the wound. Caphosol, a supersaturated calcium phosphate oral rinse, is designed, in part, to restore pH balance in the mouth. To date, a single published study supports its use for mucositis when combined with topical fluoride rinses.18

Current “Hot Topics” in Mucositis Research

Interest in the mechanism of mucosal injury continues, with additional focus on the similarities and differences between various areas of the oral cavity, digestive tract, and other mucosal surfaces. The health economics of mucosal injury and its relationship with other toxicities are increasingly under investigation, as are potential risk factors.

Conclusion

Mucositis is a complex, clinically important adverse event that is often devastating for the patient, frustrating for the healthcare professional, and expensive to manage. Viewing the oral cavity and digestive tract as a single entity can increase our understanding of the pathobiology of this phenomenon and lead to the development of a more rational, targeted treatment strategy. Future research should aim to specify the genetic risk profiles of patients and reveal the true burden of mucositis in the cancer setting. All mucosal surfaces must be considered in any management plan, along with the effects of local differentiation on the selection and scheduling of antimucotoxic therapies. The proper scheduling of antimucotoxic treatments, when fully understood, will optimize their benefit to patients. Furthermore, the variable features of mucositis throughout the oral cavity and digestive tract—and in other mucosal surfaces—must be investigated more fully. Prospective, well-designed investigations should reveal the extent of the total burden of mucositis and provide sound recommendations for effective therapy.

References


Patient Guide to

MUCOSITIS IN PATIENTS WITH CANCER

Mucositis results from a breakdown of tissues along the digestive tract, especially in the mouth, in patients with cancer who have undergone chemotherapy and/or radiation therapy. After treatment, these tissues are vulnerable to infection and heal slowly. Although mucositis may occur anywhere along the digestive tract, patients most commonly experience it as painful sores in the mouth. The condition affects 20% to 40% of patients who undergo chemotherapy and as many as half of the patients who receive a combination of radiation and chemotherapy. The severity of mucositis can be reduced by changes in diet (ask your doctor about what changes might help). Often, medications are used to promote healing.

Q & A

Q: What are the symptoms of oral mucositis?
A: Mild cases may cause only swelling of the mouth lining. This requires little or no medical intervention. Severe cases may sometimes cause extremely painful sores in the mouth. People with severe cases may also experience nausea, vomiting, and loss of appetite as a result of cancer treatments. Ask your physician about these issues before you begin your cancer therapy. Preventing mucositis is much better for patients than treating it.

Q: What can I do to prevent and/or manage mucositis?
A: Practicing good oral hygiene—brushing and flossing—is crucial to preventing mucositis. Visit your dentist for a thorough exam before you begin your cancer treatment.

Q: How is mucositis treated?
A: There are many treatment options for mucositis. Maintaining good oral hygiene—brushing and flossing—is one of the most important things patients can do. Special prescription mouthwashes can reduce swelling and reduce the risk for infection. Some antibiotics can also prevent mucositis from occurring. Talk to your doctor about these. If you do develop mucositis, saliva substitutes and new drugs that help promote regrowth of the damaged oral tissues are also available.

For more information:
The National Cancer Institute
www.cancer.gov
The National Institute of Dental and Craniofacial Research
www.nidcr.nih.gov
Medscape
www.medscape.com

Helpful Tips
- Use a soft toothbrush and brush your teeth after every meal and at bedtime
- Avoid hot, spicy foods
- Avoid mouthwashes with alcohol
- Rinse your mouth frequently with warm water
- Do not smoke or drink alcohol
- Use a saliva substitute