Complete Summary

GUIDELINE TITLE

Updated clinical practice guidelines for the prevention and treatment of mucositis.

BIBLIOGRAPHIC SOURCE(S)

Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, Migliorati CA, McGuire DB, Hutchins RD, Peterson DE, Mucositis Study Section of the Multinational Association of Supportive Care in Cancer, International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 2007 Mar 1;109(5):820-31. [58 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer 2004 May 1;100(9 Suppl):2026-46.

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SCOPE

DISEASE/CONDITION(S)

Alimentary (oral and gastrointestinal) mucositis

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Dentistry
Hematology
Nursing
Oncology
Radiation Oncology
Surgery

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Dentists
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To provide updated evidence-based clinical practice guidelines for the management (prevention and treatment) of oral and gastrointestinal mucositis in oncology patients

TARGET POPULATION

Cancer patients with alimentary (oral and/or gastrointestinal) mucositis

INTERVENTIONS AND PRACTICES CONSIDERED

Prevention

Oral Mucositis

1. Radiotherapy
    - Use of midline radiation blocks and 3-dimensional radiation treatment
    - Benzydamine
2. Standard-dose chemotherapy
    - Oral cryotherapy
3. High-dose chemotherapy with or without total body irradiation plus hematopoietic stem cell transplantation
    - Keratinocyte growth factor-1 (palifermin)
    - Cryotherapy
    - Low-level laser therapy

Gastrointestinal Mucositis

1. Radiotherapy
    - Sulfasalazine
    - Amifostine
2. Standard-dose and high-dose chemotherapy
    - Ranitidine and omeprazole
    - Systemic glutamine
3. Combined chemotherapy and radiotherapy
    - Amifostine

Management/Treatment

Oral Mucositis

1. Development and evaluation of oral care protocols
    - Soft toothbrush
    - Validated tools for regular assessment of oral pain and oral cavity health
    - Patient and staff education
2. Inclusion of dental profession through treatment and follow-up
3. Patient controlled analgesia with morphine

Gastrointestinal Mucositis

1. Basic bowel care and good clinical practices
2. Adequate hydration
3. Radiotherapy
    - Sucralfate enemas
4. Standard-dose and high-dose chemotherapy
    - Loperamide and octreotide

The following were considered but not recommended:

- Chlorhexidine, antimicrobial lozenges, acyclovir and its analogues, pentoxifylline, and granulocyte-macrophage–colony stimulating factor mouthwashes for the prevention of oral mucositis
- Sucralfate for treatment of oral mucositis following radiotherapy
- Chlorhexidine for treatment of oral mucositis following standard-dose chemotherapy
- Oral sucralfate, 5-amino salicylic acid and its related compounds mesalazine and olsalazine, and systemic glutamine for prevention of gastrointestinal mucositis

MAJOR OUTCOMES CONSIDERED

- Gastrointestinal mucosal injury
- Oral mucosal injury
- Hydration status
- Nutritional status
- Infection
- Oral cavity health
- Oral pain

- Proctitis

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Using the Ovid interface to Medline and a publication time frame of January 2002 to May 2005, the guideline developers retrieved 3974 articles, only 622 of which were of sufficient quality and relevance to be included in the final recommendations. At the time of the search, *mucositis* was not a Medical Subject Heading (MeSH); thus, the guideline developers searched for *mucositis* as a text word in article titles and abstracts. The following terms were also searched to identify all publications that had addressed mucositis: *stomatitis*, a MeSH that was exploded to include related terms of *Stevens-Johnson syndrome* and *stomatitis* (*aphthous, denture, herpetic*); *mucous membrane*, a MeSH that was exploded to include related terms of g*astric mucosa, goblet cells, intestinal mucosa, mouth mucosa*, and *respiratory mucosa*.

Terms were modified further with *pathology*, *pathophysiology*, and *radiation effects and injury* to narrow the retrieval to publications in which the mucosa was injured and to limit the search to specific subject areas that were assigned to the various reviewers. By exploding the MeSH term *neoplasms*, the search was limited to neoplastic disease. The final step was to limit the retrieval to articles that were written in English.

The medical librarian conducted separate literature reviews, working closely with the group leaders for each of 8 subject domains: 1) epidemiology, economics, and outcome; 2) pathogenesis; 3) terminology, definition, and scales; 4) growth factors and cytokines; 5) antimicrobials, mucosal coating agents, anesthetics, and analgesics; 6) alternative and natural therapies, laser, ice, etc; 7) basic oral care, bland rinses, protocol development and education, and good clinical practice; and 8) anti-inflammatory agents and amifostine. The group leaders reviewed both preclinical and clinical articles relating to the entire alimentary tract.

NUMBER OF SOURCE DOCUMENTS

622

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Level I evidence is reserved for meta-analyses of randomized controlled trials or randomized trials with high power.

Level II evidence includes randomized trials with lower power.

Level III evidence includes nonrandomized trials, such as cohort or case-controlled series.

Level IV evidence includes descriptive and case studies.

Level V evidence includes case reports and clinical examples.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Publications in the finalized set of literature were distributed to each group with instructions based on methods for reviewing and scoring the literature published by Hadorn et al., 1996. At least 2 panel members reviewed each article. Preclinical studies were not used to create guidelines per se; rather, they were used as indicators of future directions for preclinical and clinical studies.

The systematic weighting of both level and grade of evidence followed the same process that was used for the original guidelines based on criteria of the American Society of Clinical Oncology that rated the level of evidence on a scale from I to V and refined this by grading each recommendation from A to D.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The panel consisted of 30 mucositis-involved health care professionals, including oral oncologists, radiation oncologists, medical oncologists, surgeons, nurses, dentists, dental hygienists, basic scientists, epidemiologists, outcomes researchers, and a medical librarian.

Each group presented its report and draft of guideline revisions at a workshop in Geneva, Switzerland on June 27 and 28, 2005. The entire panel discussed each guideline to ensure that it met the correct standards and to achieve a consensus (see "Rating Scheme for the Strength of the Recommendations"). The current report includes the new guidelines that were developed based on this process.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Recommendation Grades

Grade A is reserved for Level I evidence or consistent findings from multiples studies of Level II, III, or IV evidence.

Grade B is for Level II, III, or IV evidence with generally consistent findings.

Grade C is similar to grade B but with inconsistencies.

Grade D implies little or no evidence.

Guideline Classification and Hierarchy*

Recommendation: A recommendation is reserved for guidelines that are based on Level I or Level II evidence.

Suggestion: A suggestion is used for guidelines that are based on Level III, Level IV, and Level V evidence; this implies panel consensus on the interpretation of this evidence.

No guideline possible: No guideline possible is used when there is insufficient evidence on which to base a guideline; this conclusion implies 1) that there is little or no evidence regarding the practice in question, or 2) that the panel lacks a consensus on the interpretation.

*Used with permission from the publisher. Adapted from: Somerfield M, Padberg J, Pfister D, et al. ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. Classic Pap Curr Comments.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The grades of recommendations (A–D) and levels of evidence (I-V) are defined at the end of the "Major Recommendations" field.

Note: The following guidelines represent the integration of the original guidelines from 2002 plus the updated guidelines developed at the Geneva, Switzerland workshop of 2005. Recommendation grades and levels of evidence for

recommendations that were not updated come from the previous version of the guideline (see the "Availability of Companion Documents" field).

Summary of Evidence-based Clinical Practice Guidelines for Care of Patients with Oral and Gastrointestinal Mucositis (2005 Update)

I. Oral Mucositis

Basic Oral Care and Good Clinical Practices

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 oral mucositis from chemotherapy and/or radiation therapy (Level III evidence, grade B suggestion). As part of the protocols, the panel suggests the use of a soft toothbrush that is replaced 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.
2. The panel recommends patient-controlled analgesia with morphine as the treatment of choice for oral mucositis pain in patients undergoing hematopoietic stem cell transplantation (HSCT) (Level 1 evidence, grade A recommendation). Regular oral pain assessment using validated instruments for self-reporting is essential.

Radiotherapy: Prevention

3. The panel recommends the use of midline radiation blocks and 3-dimensional radiation treatment to reduce mucosal injury. (Level 2 evidence, grade B recommendation)
4. The panel recommends benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy. (Level I evidence, grade A recommendation)
5. The panel recommends that chlorhexidine not be used to prevent oral mucositis in patients with solid tumors of the head and neck who are undergoing radiotherapy. (Level II evidence, grade B recommendation)
6. The panel recommends that antimicrobial lozenges not be used for the prevention of radiation-induced oral mucositis. (Level II evidence, grade B recommendation)

Radiotherapy: Treatment

7. The panel recommends that sucralfate not be used for the treatment of radiation-induced oral mucositis. (Level II evidence, grade A recommendation)

Standard-Dose Chemotherapy Prevention

8. The panel recommends that patients receiving bolus 5-fluorouracil (5-FU) chemotherapy undergo 30 minutes of oral cryotherapy to prevent oral mucositis. (Level II evidence, grade A recommendation)
9. The panel suggests the use of 20 to 30 minutes of oral cryotherapy to decrease mucositis in patients treated with bolus doses of edatrexate. (Level IV evidence, grade B suggestion)
10. The panel recommends that acyclovir and its analogues not be used routinely to prevent mucositis. (Level II evidence, grade B recommendation)

Standard-Dose Chemotherapy: Treatment

11. The panel suggests that chlorhexidine not be used to treat established oral mucositis. (Level III evidence, grade C recommendation)

High-Dose Chemotherapy With or Without Total Body Irradiation Plus HCST: Prevention

12. In patients with hematologic malignancies who are receiving high-dose chemotherapy and total body irradiation with autologous stem cell transplantation, the panel recommends the use of keratinocyte growth factor-1 (palifermin) in a dose of 60 micrograms/kg per day for 3 days prior to conditioning treatment and for 3 days posttransplantation for the prevention of oral mucositis. (Level 1 evidence, grade A recommendation)
13. The panel suggests the use of cryotherapy to prevent oral mucositis in patients receiving high-dose melphalan. (Level II evidence, grade A recommendation)
14. The panel does not recommend the use of pentoxifylline to prevent mucositis in patients undergoing HSCT. (Level II evidence, grade B recommendation)
15. The panel suggests that granulocyte macrophage colony-stimulating factor (GM-CSF) mouthwashes not be used for the prevention of oral mucositis in patients undergoing HSCT. (Level II evidence, grade C recommendation)
16. The panel suggests the use of low-level laser therapy (LLLT) to reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before HSCT if the treatment center is able to support the necessary technology and training, because LLLT requires expensive equipment and specialized training. Because of interoperator variability, clinical trials are difficult to conduct, and their results are difficult to compare; nevertheless, the panel is encouraged by the accumulating evidence in support of LLLT. (Level II evidence, grade B recommendation)

II. Gastrointestinal (GI) Mucositis

Basic Bowel Care and Good Clinical Practices

17. The panel suggests that basic bowel care should include the maintenance of adequate hydration, and that consideration should be given to the potential for transient lactose intolerance and the

presence of bacterial pathogens. (Level IV evidence, grade D suggestion)

Radiotherapy: Prevention

18. The panel suggests the use of 500 mg sulfasalazine orally twice daily to help reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis. (Level II evidence, grade B recommendation)
19. The panel suggests that amifostine in a dose $\geq$340 mg/m^2 may prevent radiation proctitis in patients who are receiving standard-dose radiotherapy for rectal cancer. (Level III evidence, grade B suggestion)
20. The panel recommends that oral sucralfate not be used to reduce related side effects of radiotherapy; it does not prevent acute diarrhea in patients with pelvic malignancies undergoing external beam radiotherapy; and, compared with placebo, it is associated with more GI side effects, including rectal bleeding. (Level I evidence, grade A recommendation)
21. The panel recommends that 5-amino salicylic acid and its related compounds mesalazine and olsalazine not be used to prevent GI mucositis. (Level I evidence, grade A recommendation)

Radiotherapy: Treatment

22. The panel suggests the use of sucralfate enemas to help manage chronic radiation-induced proctitis in patients who have rectal bleeding. (Level III evidence, grade B suggestion)

Standard-Dose and High-Dose Chemotherapy: Prevention

23. The panel recommends either ranitidine or omeprazole for the prevention of epigastric pain after treatment with cyclophosphamide, methotrexate, and 5-FU or treatment with 5-FU with or without folinic acid chemotherapy. (Level II evidence, grade A recommendation)
24. The panel recommends that systemic glutamine not be used for the prevention of GI mucositis. (Level II evidence, grade C recommendation)

Standard-Dose and High-Dose Chemotherapy: Treatment

25. When loperamide fails to control diarrhea induced by standard-dose or high-dose chemotherapy associated with HSCT, the panel recommends octreotide at a dose $\geq$100 micrograms subcutaneously, twice daily. (Level II evidence, grade A recommendation)

Combined Chemotherapy and Radiotherapy: Prevention

26. The panel suggests the use of amifostine to reduce esophagitis induced by concomitant chemotherapy and radiotherapy in patients with nonsmall cell lung cancer. (Level III evidence, grade C suggestion)

Definitions:

Levels of Evidence

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CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for the updated recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate management of alimentary mucositis, which may lead to decreased burden of illness associated with oral and gastrointestinal mucositis, including:

- Relief of pain
- Improved outcomes of cancer therapy by preventing breaks in therapy or reduction of dose due to mucositis
- Less mucosal injury
- Improved hydration and nutritional status
- Prevention of infection

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

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IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Outcomes Assessment

In recognition of the importance and challenge of disseminating and using these guidelines in clinical oncology practice, the review team is considering cooperative strategies with other professional oncology organizations as well as methodologies to assess the scope and durability of the impact of the guidelines on clinical practice.

IMPLEMENTATION TOOLS

Foreign Language Translations
Slide Presentation

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Keefe DM, Schubert MM, Elting LS, Sonis ST, Epstein JB, Raber-Durlacher JE, Migliorati CA, McGuire DB, Hutchins RD, Peterson DE, Mucositis Study Section of the Multinational Association of Supportive Care in Cancer, International Society for Oral Oncology. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 2007 Mar 1;109(5):820-31. [58 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 (revised 2008 Feb)

GUIDELINE DEVELOPER(S)

International Society for Oral Oncology - Disease Specific Society
Multinational Association of Supportive Care in Cancer - Disease Specific Society

SOURCE(S) OF FUNDING

Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology

GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

The costs for the workshop and for administrative assistance in guideline preparations were paid from unrestricted educational grants made to the Mucositis Study Group of Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO). No representatives from any of the companies that provided grants attended the workshop, nor were they allowed access to the guidelines prior to publication. The guideline development process was determined entirely by the panel. Each panel member completed a conflict-of interest disclosure form that revealed all relationships with pharmaceutical companies that could be affected by the development and publication of these guidelines.

Mark M. Schubert is currently an advisory board participant for MGI Pharma and on the speakers' bureau (Kepivance) for Amgen; previously he has served as an advisory board participant for McNeil Pharmaceuticals and on the speakers' bureau for OSI.

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GUIDELINE AVAILABILITY

Electronic copies: Available from the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Summary of evidence-based clinical practice guidelines for care of patients with oral and gastrointestinal mucositis (2005 update). Available in English and Greek from the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) Web site.
- Mucositis guidelines update. Slide presentation. Electronic copies: Available from the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) Web site.
- Rubenstein EB, Peterson DE, Schubert M, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004 May 1;100(9 Suppl):2026-46. Electronic copies: Available from the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) Web site.

PATIENT RESOURCES

None available

NGC STATUS

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