MASCC/ISOO
Mucositis Management Guidelines: Update 2005

Dorothy M K Keefe
Chairman, Mucositis Study Group
On behalf of the 2005 Review Team
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<th>Reviewers and topics</th>
<th>Topics</th>
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<td>Epidemiology, Economics and Outcome:</td>
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<td>Pathogenesis: Steve Sonis</td>
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<td>• Richard Logan</td>
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<td>• Inger von Butzlingslowen</td>
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<td>• Mike Brennan</td>
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<td>Analgesics, anaesthetics, Mucosal coating agents &amp; antimicrobials: Joel Epstein</td>
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<td>• Andrei Barasch</td>
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<td>• Kathryn Damato</td>
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<td>• Sharon Elad</td>
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<td>• Arnold Altman</td>
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<td>Alternative &amp; Natural, Laser, Ice: Cesar Migliorati</td>
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<td>• Loree Oberlee-Edwards</td>
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<td>Basic Oral care, bland rinses, GCP, protocol &amp; education: Debbie McGuire</td>
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<td>• Judi Johnson</td>
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<td>• Patricia Wienandts</td>
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<td>• Elvira Correa</td>
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<td>Anti-inflammatories, Amifostine: Mark Schubert</td>
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<td>• Rene-Jean Bensadoun</td>
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<td>• Raj Lalla</td>
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Literature Review

Extremely fortunate to have services of Ron Hutchins again
  Corporate memory
  Knowledge of IT improvements
  Enthusiasm for project
Sponsors

Without whom we couldn’t have done this

Novartis
MGI Pharma
Curagen
RxKinetics
Laclede

Many thanks to all concerned.
Changes since last time

• Whole-tube paradigm
• Mechanistic based therapies
• Enhanced understanding of epidemiology and pathobiology as a result of previous efforts
• Each group looks at clinical and pre-clinical
Constellation of Symptoms & Clinical Manifestations of GI Mucositis

- Pain
  - Distension
  - Nausea
  - Dysphagia
  - Reduced Oral Intake
    - Weight Loss/Malnutrition
      - Fatigue
      - Electrolyte Imbalance
      - Malabsorption

- Diarrhea
  - Systemic Infection
    - Bleeding
    - Colonization
      - Ulceration

- Weight Loss/Malnutrition
- Fatigue
- Electrolyte Imbalance
- Malabsorption
- Systemic Infection
- Colonization
- Ulceration
- Bleeding
- DEATH
Similarities

Evidence Based Guidelines
Sommerfield and Hadorn papers as guides
English only

Also:
May 2002-May 2005
Feb 2002-May 2005 for Epidemiology

>3000 publications in that time
Process

• Leadership group met in Miami before MASCC 2004
  ▪ Strategic planning
  ▪ Need for Guidelines Update

• Series of teleconferences in 2004/2005
  ▪ Invited reviewers
  ▪ Looked at scope of literature
  ▪ Changes in strategy from version 1
  ▪ Planned face-to-face meetings

• Each group leader did separate literature review with Ron Hutchins, but included whole alimentary canal
Process

• Leadership group meeting Orlando May 12\textsuperscript{th} 2005
  ▪ Ironed-out problems
  ▪ Finalized papers for review
  ▪ Allocated teams based on size of issue & expertise
  ▪ Fine-tuned review methodology & instructions
  ▪ Developed publication strategy
  ▪ Began planning for next update
  ▪ Set reviewers to work!
# Guideline Classification/Hierarchy

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td><strong>Recommendation</strong></td>
<td>A recommendation is reserved for guidelines that are based on Level I or Level II evidence.</td>
</tr>
<tr>
<td><strong>Suggestion</strong></td>
<td>A suggestion is used for guidelines that are based on Level III, Level IV, &amp; Level V evidence; this implies panel consensus on the interpretation of this evidence.</td>
</tr>
</tbody>
</table>
| **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 of existing evidence. |
Publication Strategy

• Single ‘master paper’ to update the original Cancer Supplement
• MASCC website
• Set of papers for Journal of Supportive Care in Cancer
  ▪ We have learned from our Anti-emetic colleagues!
• Updates every 3 years
  ▪ Web-based review process next time
  ▪ Data-base of papers reviewed
  ▪ We have approached ASCO about endorsement
Impact of 1st version of guidelines

- Increased our understanding of epidemiology & pathobiology
- Stimulated interest in this area of research
  - Number of Mucositis abstracts
  - Quality of research
  - Number of people in this area
- Launching pad for the future
- May even be beginning to help the patients!
Terminology and Assessment

• Medical Subject Heading (MeSH) recommendation:
  ▪ proposal submitted February 2005
  ▪ Natl Libr Med. decision anticipated by September 2005

• Key areas:
  ▪ Historical context (NIH, MASCC/ISOO, ASCO)
  ▪ Addition of section for Terminology
  ▪ Terminology and Assessment paradigm (e.g., pediatric)
Pathobiology Update
Healing Ulceration Signaling and Amplification Upregulation and Message Gen Initiation Tissue Injury DNA Injury Fibronectin Breaks Up Activates Macrophages MMP IL-1β IL-6 TNF-α Gene Upregulation Expression of Adhesion Molecules COX-2 Angiogenesis Ceramide Pathway Apoptosis Tissue Injury Sphingomyelinase Clonogenic Cell Death ROS Cell Membrane Epithelium Endothelium Macrophages Connective Tissue CT CTCT Today's Pathobiology Perspective: A Multiple Mechanism Model
When Is the Optimum Time for Mechanistically Based Intervention?

- Mechanism-specific Suppressors
  - Proliferative, rate-dependent, epithelial injury
  - Resolution of acute wound

- Damage Control Agents
  - 1 to 10 days

- Healing Accelerators
  - 1 to 14 days

- Cell Resistance Modifiers
  - 24h

- Molecular, cellular & tissue events leading to epithelial stem cell injury

Chemotherapy
PROCESS:

1. Identification of Generic vs Tissue Specific drivers of mucotoxicity

2. Genetic v Non Genetic control

3. Evidence based grading

4. Hierarchical characterization
## GENETICALLY CONTROLLED ELEMENTS

<table>
<thead>
<tr>
<th>GENERIC</th>
<th>TISSUE SPECIFIC</th>
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<tbody>
<tr>
<td>Transcription Factors</td>
<td>Trefoils</td>
</tr>
<tr>
<td>Proinflammatory Cytokines</td>
<td>Defensins</td>
</tr>
<tr>
<td>Mediators (Caspases etc)</td>
<td>Secretins</td>
</tr>
<tr>
<td>Drug Metabolism</td>
<td>Luminal secretions</td>
</tr>
<tr>
<td>Gender response to hormone Levels</td>
<td>Differential response to RT/CT</td>
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<tr>
<td>Susceptibility to apoptosis and rate</td>
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<tr>
<td>Oxidative Pathways</td>
<td></td>
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<tr>
<td>Folate/B12 Deficiencies</td>
<td></td>
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<tr>
<td>Ethnicity</td>
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R = Real data  
H = Hypothetical  
T = Teleological
<table>
<thead>
<tr>
<th>Generic</th>
<th>Tissue Specific</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Epithelial type and characteristics</td>
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<tr>
<td>Circadian variables</td>
<td>Intrinsic endocrine system</td>
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<tr>
<td>Underlying pathology</td>
<td>Local microbial environment</td>
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<tr>
<td>SLE / other autoimmune disease, diabetes,</td>
<td>Tumor effect</td>
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<tr>
<td>others</td>
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</table>

R = Real  H = Hypothetical  T = Teleological
Hierarchical Analysis

GLOBAL

TISSUE

CELLULAR

INJURY

MOLECULAR
Hierarchical Analysis

GLOBAL – defines baseline susceptibility

- Underlying pathology
- Circadian / seasonal effects
- Gender
- Tumor effect
- Agent / metabolites
- Combined Modalities – CT / RT
Hierarchical Analysis

TISSUE / CELLULAR

- ROS
- Trefoils
- Defensins
- Secretins
- Luminal secretions
- Local immune response
- Local microbial environment
- Apoptosis susceptibility
- Metabolism
- Neuroendocrine loop
Hierarchical Analysis

MOLECULAR

- Clonogenic cell death
- Transcription factors
- Mediators
  - Proinflammatory cytokines
  - Caspases
  - MMPs
  - Leukotrienes and other cytokines (VEGFs, IL-13, etc.)
  - Ceramide
- Signaling from ECM
Hierarchical Analysis

INJURY

Epithelial type / character
threshold
Tissue environmental filters
Hierarchical Analysis

GLOBAL

TISSUE

CELLULAR

MOLECULAR

INJURY
Epidemiology Update
## Epidemiology Group 2005 Update – Gaps that we filled

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Regimen</th>
<th>Dosing</th>
<th>Number papers</th>
<th>Topic Status</th>
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<td>NH Lymphoma</td>
<td>CHOP, CHOPR</td>
<td>Dose dense</td>
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<td>CHOEP</td>
<td>Dose Dense</td>
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<td>Breast</td>
<td>AC, AC-T</td>
<td>Dose Dense</td>
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<td>New</td>
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<td>Update</td>
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<td>Lung</td>
<td>Carbo + taxane, gemcitabine + taxane, +/- RT</td>
<td>Adjuvant, Neoadjuvant, Met</td>
<td>40 – 84</td>
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<td>CRC</td>
<td>Folfox, Folfiri</td>
<td>Standard</td>
<td>10</td>
<td>Update</td>
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<td>Econ, Outcomes</td>
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<td>10</td>
<td>Update</td>
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<tr>
<td>Bladder</td>
<td>MVAC</td>
<td>Dose Dense</td>
<td>ADD</td>
<td>New</td>
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Gaps That Remain

• Targeted/Biological therapies
  Single Agent
  Combination
• Capecitabine
• RT
• Myeloma – Standard therapy
• Mini-transplant

GCSF
Steroid use with Taxanes, CHOP
Basic Oral Care
Bland Rinses
Protocols & Education
Good Clinical Practice
Guidelines: Oral Mucositis

- Oral care protocols/education
  - UPDATED

Guideline:

- Suggest performing basic oral care including using a soft toothbrush with regular replacement of the toothbrush
Oral Mucositis

Midline radiation blocks & 3-D radiation treatment

- (recommended)

- NO CHANGE
Bland Rinses

Guideline:
- *No guideline possible* (insufficient evidence)

— *NO CHANGE*
Original Guideline:

- *Suggest* use of oral care protocols that include patient education

**Update**: *Suggest* that protocol development be interdisciplinary. Education should include staff, and quality improvement processes should be used to evaluate protocols and education.
Good Clinical Practice (GCP)

Pain management

Oral assessment and oral care

Dental care:
  - Pre-treatment, during treatment, follow-up

Notes:
  - staff, patient, and family education should be integrated in all areas
  - outcome assessment using quality improvement process is important
Lower GI mucositis: GCP

**HISTORY**
- **“Normal” bowel function**
  - Frequency
  - Consistency
  - Colour
- **Current bowel function**
  ± Duration of change
  - Frequency
  - Consistency
  - Blood
  - Mucus
- **Other symptoms**
  - Nausea/vomiting
  - ↓ Oral intake – fluid
    - solid
  - Exacerbating features
  - Fever/chills
  - Abdominal pain – location
    - nature
  - Weight loss
  - Bloating
- **Drug treatment**
  - Chemo/Analgesics/Antibiotics

**PATIENT STATUS**
- Hydration
- Abdominal examination
- Bowel sounds
- Rectal examination

**EXAMINATION**
- Stool frequency
- Consistency
- Colour
  → Culture

**ACTION**
- Maintain hydration
- Optimise motility of gut
- Do you need to ↓ secretion
  - osmolality
  - treat infection

**AXR**
- Obstruction
- Bowel wall thickening
Treatment

Diarrhoea

- **Iloperamide**
  - 2 stat +
  - 1 with each loose stool
  - Maximum 1/day

- **Reduce dairy intake**

- **Re-hydrate**
  - (oral or IV fluids)

If no response

**Octreotide**
- at least
- 100µg bd s/c
Guidelines: Diarrhea

- Octreotide (at least 100 µg sc bd)
  - for PTS receiving high-dose CT with stem cell support (recommended)

- NO CHANGE
Anti-inflammatory Agents
Amifostine
Guidelines: Oral Mucositis

- **Benzydamine**
  - for prevention of RT induced mucositis in PTS with H&N CA receiving moderate dose RT (recommended)

- NO CHANGE

- Note closure of trial in North America
Anti Inflammatory Agents

- Clinical Studies
  - Misoprostol
  - Orgotein
  - Irsogladine
  - Flurbiprophen
  - Allopurinol Ice Balls

- No Guideline Possible for any of these
  - Insufficient evidence
Amifostine

- to reduce esophagitis induced by CT/RT in PTS with NSCLC (suggested)

New Guideline:
Multiple small studies have been performed, and the results are still conflicting.

Insufficient evidence to upgrade to recommendation
May need to be downgraded to “No guideline possible”
Amifostine

- Chemotherapy in lung cancer
- Transplantation
- Head and Neck Cancer Radiotherapy
- Head and Neck Cancer Chemotherapy

- All have conflicting studies with insufficient evidence for a guideline
Amifostine

• However,
  - Prophylaxis of radiation proctitis
  - 4 studies
  - All small
  - But all in favour of amifostine

  It is *suggested* that amifostine in a dose of at least 340mg/kg may prevent radiation proctitis in those receiving standard dose RT for rectal cancer.
Guidelines: Upper GI Mucositis

- Ranitidine or omeprazole
  - for the prevention of epigastric pain post-Treatment with CMF or 5-FU +/- folinic acid (recommended)

- NO CHANGE
Antimicrobials
Analgesics
Anaesthetics
Mucosal Coating Agents
Nutritional Supplements
Guidelines: Oral Mucositis

NOT Recommended:

- Chlorhexidine
  - to prevent OM in PTS with H&N CA undergoing RT or to treat established OM

- Acyclovir/analogues
  - to prevent mucositis

- Pentoxifylline
  - to prevent OM in PTS undergoing HDCSCT

- NO CHANGE
Guidelines: Pain

- PCA with morphine for oral mucositis pain in PTS undergoing HSCT (recommended)

- NO CHANGE
Antimicrobial lozenges

- Polymixin tetracycline Amphotericin B (PTA)
- Bacitracin Clotrimazole Gentamicin (BCoG)

- H&N RT, Adults, Prevention
- Results: equal to placebo
- Previous Guideline: Insufficient evidence for treatment

- New Guideline: Recommend against use for prevention
Sucralfate

• RT or CT, Adults, Prevention
• Results: no difference in incidence, severity and duration of oral mucositis and pain
• Previous Guideline: no guideline possible

• Current Guideline:
  - Chemotherapy: No Guideline Possible
  - Radiotherapy: It is *recommended* that sucralfate *not* be used for the prevention of RT-induced oral mucositis
Guidelines: Lower GI/Pelvic Muco...

- Sulphasalazaine (500 mg orally bd)
  - for PTS receiving external beam RT to the pelvis (suggested)
- Sucralfate enemas
  - for the management of chronic RT induced proctitis in PTS with rectal bleeding (suggested)

- NO CHANGE
Guidelines: Lower GI/Pelvic Mucositis

NOT Recommended:

- Oral sucralfate
  - to prevent acute diarrhea in PTS with pelvic malignancies undergoing external beam RT
- 5-amino salicylic acid, mesalazine, & olsalazine
  - to prevent GIM
- NO CHANGE
Nutritional supplements

Glutamine

**Previous Guideline**: insufficient evidence for treatment of GI mucositis

**Current Guideline**: suggestion against use of systemic glutamine for prevention

Future Directions: Saforis
Laser
Cryotherapy
Alternative therapy
Cryotherapy

- **Original Guideline:**
  - The use of cryotherapy is *recommended* for prevention of mucositis in:
    - Bolus 5 FU and Leucovorin/5FU
  - *Suggested* for Editronate

- **New Guideline, as before plus:**
  - *Suggested* for high dose Melphalan in HSCT
The use of laser is suggested for the prevention of RT induced oral mucositis. Mechanism of action still speculative with no good support of scientific evidence.
Alternative therapy

- Vitamin A
- Glutamine
- Vitamin E
- Vit B12, Folate, and Diet supplm -
- Aloe Vera
- PV701 – Milk-Derived Protein Extract
- No Guideline possible
  - Conflicting and insufficient evidence
Cytokines and Growth Factors
### Agents in pre-clinical study

- IL-11
- KGF-1 (Palifermin)
- KGF-2
- FGF-20 (Velafermin)
- GLP-2
- Whey Growth Factor Extract (WGFE)
- RDP58 (anti-pro-inflammatory cytokine)
Agents in Clinical Trial

- **IL-11**
  - trials stopped early for excess toxicity
- **GM-CSF**
  - Still no evidence that it reduces oral mucositis
- **G-CSF**
  - Still no evidence that it reduces oral mucositis
- **KGF-2**
  - Withdrawn by company
- **Velafermin**
  - In Phase II trial
A Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial of Palifermin for Reduction of Mucositis in Patients With Hematologic Malignancies Undergoing TBI With High-Dose Chemotherapy With Auto-PBPCT

PBPCT, peripheral blood progenitor cell transplantation; TBI, total body irradiation

Palifermin Phase 3 Study Schema

Placebo
Stratified by center and primary disease
Palifermin

= single IV dose of study drug (60 µg/kg/day palifermin or placebo)

Patient Characteristics (N=212)

**Primary Disease**

- **HD** 21%
- **NHL** 67%
- **Multiple Myeloma** 9%
- **AML** 2%
- **ALL** 0.5%
- **CLL** 0.5%

**CD34+ cells infused median** (x 10⁶/kg)

- **Placebo**: 5.0
- **Palifermin**: 5.2

**Gender (M/F)**

- Palifermin: 59/47
- Placebo: 72/34

**Karnofsky PS ≥80%**

- Palifermin: 97%
- Placebo: 99%

**Median age (range)**

- Palifermin: 48 (18–69)
- Placebo: 49 (19–68)


Duration of Severe Oral Mucositis

Mean (Days)

Placebo (n=106) 10.4
Palifermin (n=106) 3.7

P<0.001
Difference (95% CI)
6.7d (5.3, 8.0)

Oral Mucositis Incidence

Placebo (n=106)
- Grade 4: 100%
- Grade 3: 80%
- Grade 2: 60%
- Grade 1: 40%
- Grade 0: 20%

Palifermin (n=106)
- Grade 4: 100%
- Grade 3: 80%
- Grade 2: 60%
- Grade 1: 40%
- Grade 0: 20%

Incidence and Duration of Grade 4 Mucositis

Parenteral Opioid Analgesic Use

**Duration (days, median)**
- Placebo: 11 days, median
- Palifermin: 7 days, median

**Morphine Equivalents (mg, median)**
- Placebo: 535 mg, median
- Palifermin: 212 mg, median

### Adverse Events Related to Study Drug

<table>
<thead>
<tr>
<th>Study drug-related, pre-TBI dosing</th>
<th>Incidence</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>n = 106</td>
<td>Palifermin</td>
</tr>
<tr>
<td>Skin erythema, pruritus, edema, tongue “feeling thick,” taste disturbances*</td>
<td>3%</td>
<td>26%</td>
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<tr>
<td>Transient, asymptomatic increases beyond ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>67%</td>
<td>77%</td>
</tr>
<tr>
<td>Lipase</td>
<td>25%</td>
<td>32%</td>
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</tbody>
</table>

*Severe in 1 patient of each group; all other mild/moderate. ULN = upper limit of normal

Survival-Autotransplant Studies: Palifermin vs Placebo

Kaplan-Meier Survival Curves by Treatment

Palifermin (KGF1)

• Original Guideline:
  - No Guideline Possible (insufficient evidence)

• New Guideline:
  - In patients with haematological malignancies, receiving high dose chemotherapy and TBI with autologous stem cell transplant, the use of Palifermin in a dose of 60 µg/kg/day for 3 days prior to conditioning treatment and for 3 days post transplant is recommended for the prevention of oral mucositis.
    - Level I, Grade A evidence
Ideal Study Design for assessing mucositis intervention:

- Multicenter, double-blind, prospective, adequately powered, randomized controlled study
- Defined populations: patient (pediatric, geriatric) disease status and its therapy
- Validated tools for outcome assessments
- Account for potential confounding factors:
- Appropriate analysis
Summary

• We have now completed the 1st update of the Mucositis Management Guidelines
  ▪ The original version was a great launching pad
  ▪ Rapid Progress is being made in the understanding of this complex problem
  ▪ We have much work still to do to fully fix the problem & reduce the negative impact of cancer treatment

▪ For the first time, we have active agents in this area