Pain Management of Oral Mucositis in Children

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Disclosures

• None
Objectives:

• Review evidence-based guidelines for OM prevention & treatment
  – MASCC/ISOO Clinical Practice Guidelines v.2 (2014)
• Discuss approaches to assess and manage mucositis pain in children
• Briefly review recent RCT and Clinical Trials on OM in children
Main Strategies Used to Manage Chemotherapy or Radiation-induced OM

- Oral care protocols
- Antimicrobial agents (chlorhexidine)
- Anti-inflammatory agents (benzydamine)
- Cytoprotective agents (glutamine)
- Biological response modifiers (palifermin)
- Physical therapies (cryotherapy and PBM)
- Anesthetics
- Analgesics (opioids for pain management)
Main Strategies Used to Manage Chemotherapy or Radiation-induced OM

- Oral care protocols
- Antimicrobial agents (chlorhexidine)
- Anti-inflammatory agents (benzydamine)
- Cytoprotective agents (glutamine)
- Biological response modifiers (palifermin)
- Physical therapies (cryotherapy and laser)
- Anesthetics
- Analgesics (opioids for pain management)
Evidenced-based Clinical Practice Guidelines of the Mucositis Study Group of MASCC/ISOO

• First published in 2004; most recently updated in 2014
  — The leading clinical practice guidelines for mucositis care

• 7 sections on Oral mucositis (and 1 on GI):
  1. Basic oral care
  2. Growth factors and cytokines
  3. Anti-inflammatory agents
  4. Antimicrobials, coating agents, anesthetics, and analgesics
  5. Laser and other light therapy (photobiomodulation, PBM)
  6. Cryotherapy
  7. Natural and miscellaneous agents

• Based on systematic reviews of the evidence for various interventions
  • 8279 articles identified → 1032 for detailed review → 570 qualified final
### TABLE 1. Criteria for Each Level of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from meta-analysis of multiple, well-designed, controlled studies; randomized trials with low false-positive and false-negative errors (high power).</td>
</tr>
<tr>
<td>II</td>
<td>Evidence obtained from at least 1 well-designed experimental study; randomized trials with high false-positive and/or false-negative errors (low power).</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, quasi-experimental studies such as nonrandomized, controlled single-group, pretest-postest comparison, cohort, time, or matched case-control series.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies.</td>
</tr>
<tr>
<td>V</td>
<td>Evidence obtained from case reports and clinical examples.</td>
</tr>
</tbody>
</table>

### TABLE 2. Criteria for Each Guideline Category

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Suggestion</th>
<th>No guideline possible</th>
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<tbody>
<tr>
<td>Reserved for guidelines that are based on level I or level II evidence.</td>
<td>Used for guidelines that are based on level III, level IV, and level V evidence; this implies panel consensus regarding the interpretation of this evidence.</td>
<td>Used when there is insufficient evidence on which to base a guideline; this implies 1) that there is little or no evidence regarding the practice in question, or 2) that the panel lacks consensus on the interpretation of existing evidence.</td>
</tr>
</tbody>
</table>

TABLE 4. MASCC/ISOO Clinical Practice Guidelines for Oral Mucositis

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION (i.e., strong evidence supports effectiveness in the treatment setting listed):
1. The panel recommends that 30 min of oral cryotherapy be used to prevent oral mucositis in patients receiving bolus 5-fluorouracil chemotherapy (II).
2. The panel recommends that recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) be used to prevent oral mucositis (at a dose of 60 μg/kg per day for 3 days prior to conditioning treatment and for 3 days after transplant) in patients receiving high-dose chemotherapy and total body irradiation, followed by autologous stem cell transplantation, for a hematological malignancy (II).
3. The panel recommends that low-level laser therapy (wavelength at 650 nm, power of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm²) be used to prevent oral mucositis in patients receiving HSCT conditioned with high-dose chemotherapy, with or without total body irradiation (II).
4. The panel recommends that patient-controlled analgesia with morphine be used to treat pain due to oral mucositis in patients undergoing HSCT (II).
5. The panel recommends that benzylamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).

SUGGESTIONS IN FAVOR OF AN INTERVENTION (i.e., weaker evidence supports effectiveness in the treatment setting listed):
1. The panel suggests that oral care protocols be used to prevent oral mucositis in all age groups and across all cancer treatment modalities (III).
2. The panel suggests that oral cryotherapy be used to prevent oral mucositis in patients receiving high-dose melphalan, with or without total body irradiation, as conditioning for HSCT (III).
3. The panel suggests that low-level laser therapy (wavelength around 632.8 nm) be used to prevent oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer (III).
4. The panel suggests that transdermal fentanyl may be effective to treat pain due to oral mucositis in patients receiving conventional or high-dose chemotherapy, with or without total body irradiation (III).
5. The panel suggests that 2% morphine mouthwash may be effective to treat pain due to oral mucositis in patients receiving chemoradiation for head and neck cancer (III).
6. The panel suggests that 0.5% dexamethasone and mouthwash may be effective to treat pain due to oral mucositis (IV).
7. The panel suggests that systemic zinc supplements administered orally may be of benefit to prevent oral mucositis in oral cancer patients receiving radiation therapy or chemoradiation (III).

RECOMMENDATIONS AGAINST AN INTERVENTION (i.e., strong evidence indicates lack of effectiveness in the treatment setting listed):
1. The panel recommends that PTA (polymyxin, tobramycin, amphotericin B) and BCG (bacillus Calmette-Guerin) antimicrobial lozenges and PTA paste not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (II).
2. The panel recommends that kegana antifungal mouthwash be used to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II), or in patients receiving radiation therapy or concomitant chemoradiation for head and neck cancer (II).
3. The panel recommends that sucralfate mouthwash not be used to prevent oral mucositis in patients receiving chemotherapy for cancer (II), or in patients receiving radiation therapy (II) or concomitant chemoradiation (II) for head and neck cancer.
4. The panel recommends that sucralfate mouthwash not be used to treat oral mucositis in patients receiving chemotherapy for cancer (II), or in patients receiving radiation therapy (II) for head and neck cancer.
5. The panel recommends that intravenous glutamine not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).

SUGGESTIONS AGAINST AN INTERVENTION (i.e., weaker evidence indicates lack of effectiveness in the treatment setting listed):
1. The panel suggests that chlorhexidine mouthwash not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (III).
2. The panel suggests that granulocyte-macrophage-colony-stimulating factor mouthwash not be used to prevent oral mucositis in patients receiving high-dose chemotherapy, for autologous or allogeneic stem cell transplantation (III).
3. The panel suggests that misoprostol mouthwash not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (III).
4. The panel suggests that systemic pentoxyphylline, administered orally, not be used to prevent oral mucositis in patients undergoing bone marrow transplantation (III).
5. The panel suggests that systemic pilocarpine, administered orally, not be used to prevent oral mucositis in patients receiving radiation therapy for head and neck cancer (III), or in patients receiving high-dose chemotherapy, with or without total body irradiation, for HSCT (II).

Abbreviations: Gy, gray(s); HSCT, hematopoietic stem cell transplantation; MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology; mW, milliwatt; nm, nanometers.
*Level of evidence for each guideline is in brackets after the guideline statement.
RECOMMENDATIONS IN FAVOR OF (strong evidence)

- Oral Cryotherapy x 30 min to *prevent* OM in pts receiving 5FU
- Low level laser therapy to *prevent* OM in HCT using HD chemo +/- TBI
- KGF (Palifermin) to *prevent* OM in Chemo+TBI auto-HCT for heme Ca
- Benzydamine MW to *prevent* OM in H&NC w/ moderate RT w/o chemo
- Morphine PCA to *treat* pain due to OM in pts receiving HCT
RECOMMENDATIONS IN FAVOR OF (strong evidence)

- **Oral Cryotherapy** x 30 min to *prevent* OM in pts receiving 5FU
- **Low level laser therapy** to *prevent* OM in HCT using HD chemo +/- TBI
- **KGF (Palifermin)** to *prevent* OM in Chemo+TBI auto-HCT for heme Ca
- **Benzydamine MW** to *prevent* OM in H&NC w/ moderate RT w/o chemo
- **Morphine PCA** to *treat* pain due to OM in pts receiving HCT
# Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care  
2. Growth factors and cytokines  
3. Anti-inflammatory agents  
4. Antimicrobials, coating agents, anesthetics, and analgesics  
5. Laser and other light therapy (PBM)  
6. Cryotherapy  
7. Natural and miscellaneous agents

<table>
<thead>
<tr>
<th>Evidence Strength</th>
<th>FOR</th>
<th>AGAINST</th>
</tr>
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<tbody>
<tr>
<td>Strong</td>
<td><strong>Recommends</strong></td>
<td><strong>Do NOT use</strong></td>
</tr>
<tr>
<td>Weaker</td>
<td><strong>Favors</strong></td>
<td><strong>Did NOT support</strong></td>
</tr>
<tr>
<td>Insufficient</td>
<td>No Guideline possible</td>
<td></td>
</tr>
</tbody>
</table>
Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care
   - **Favors oral care protocols** (toothbrushing, flossing, daily mouth rinse) for all to **prevent** OM
   - **Do NOT use Chlorhexidine** (at least not for H&NC RT) to **prevent** OM

2. Growth factors and cytokines
3. Anti-inflammatory agents
4. Antimicrobials, coating agents, anesthetics, and analgesics
5. Laser and other light therapy (PBM)
6. Cryotherapy
7. Natural and miscellaneous agents

Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care
   - **Favors oral care protocols** (toothbrushing, flossing, daily mouth rinse) for all to *prevent* OM
   - **Do NOT use Chlorhexidine** (at least not for H&NC RT) to *prevent* OM
   - No guideline about which *mouth rinse* is best → use anything regularly

2. Growth factors and cytokines
3. Anti-inflammatory agents
4. Antimicrobials, coating agents, anesthetics
5. Laser and other light therapy (PBM)
6. Cryotherapy
7. Natural and miscellaneous agents
Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care

2. Growth factors and cytokines
   - **Recommends** KGF (Palifermin) to *prevent* OM in HD chemo + TBI HCT for heme Cancers
   - **Did NOT support** GM-CSF to *prevent* OM in HD chemo for auto- or allo- HCT
   - No guidelines for many others

3. Anti-inflammatory agents

4. Antimicrobials, coating agents, anesthetics, and analgesics

5. Laser and other light therapy (PBM)

6. Cryotherapy

7. Natural and miscellaneous agents

GM-CSF and KGF for other settings
- Fibroblast GF-20
- KGF-2
- GCSF
- Transforming GF-beta
- Epidermal GF
- Milk-derived GF extract
- IL-11
- ATL-104
- rHu-intestinal trefoil factor
Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care
2. Growth factors and cytokines
3. Anti-inflammatory agents
   - **Recommends** Benzydamine MW to *prevent* OM in RT for H&NC (< 50 Gy) w/o chemo
     - No guideline to extend to RT >50 Gy
   - **Did NOT support** Misoprostil MW to *prevent* OM in RT for H&NC
     - No guideline about Amifostine to *prevent* OM nor others
4. Antimicrobials, coating agents, anesthetics, and analgesics
5. Laser and other light therapy (PBM)
6. Cryotherapy
7. Natural and miscellaneous agents

Aspirin
Orgotein
Azelnastine
Mesalazine
Prostaglandin E2
Immunoglobulins
Corticosteroids
Indomethacin
Flurbiprofen
Histamine
Colchicine
Placentrex
Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care
2. Growth factors and cytokines
3. Anti-inflammatory agents
4. Antimicrobials, coating agents, anesthetics, and analgesics
   - **Recommends** Morphine PCA to **treat** OM pain
   - **Favors** Fentanyl patch, Morphine MW and Doxepine MW to **treat** OM pain in specific settings
   - **Do NOT use** Antimicrobial lozenge & pastes (PTA, BCoG) to **prevent** OM w/ RT for H&NC
   - **Do NOT use** Iseganan MW to **prevent** OM w/ HD chemo ± TBI for HCT or RT +/- chemo H&NC
   - **Did NOT support** Sucralfate to **prevent or treat** OM w/ chemo or RT for H&NC
   - No guideline possible for any anesthetic nor many other agents
5. Laser and other light therapy (PBM)
6. Cryotherapy
7. Natural and miscellaneous agents
Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care
2. Growth factors and cytokines
3. Anti-inflammatory agents
4. Antimicrobials, coating agents, anesthetics, and analgesics
5. Laser and other light therapy (PBM)
   - **Recommends** Low level laser therapy to *prevent* OM in HCT using HD chemo +/- TBI
   - **Favors** Low level laser therapy to *prevent* OM in RT alone (w/o chemo) for H&NC
   - No guideline for LLLT in other settings or for *other emerging light Tx* to *prevent or treat* OM
6. Cryotherapy
7. Natural and miscellaneous agents
Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care
2. Growth factors and cytokines
3. Anti-inflammatory agents
4. Antimicrobials, coating agents, anesthetics, and analgesics
5. Laser and other light therapy (PBM)

6. Cryotherapy
   - Recommends cryotherapy to prevent OM with bolus dosing of 5-Fluorouracil
   - Favors cryotherapy to prevent OM with HD Melphalan in HCT +/- TBI
   - No guideline for cryotherapy in other settings due to inadequate evidence

7. Natural and miscellaneous agents
Summary of MASCC/ISOO Clinical Guidelines

1. Basic oral care
2. Growth factors and cytokines
3. Anti-inflammatory agents
4. Antimicrobials, coating agents, anesthetics, and analgesics
5. Laser and other light therapy (PBM)
6. Cryotherapy
7. Natural and miscellaneous agents
   - Favors zinc to prevent OM with chemo +/- RT for oral cancer
   - Do NOT use IV Glutamine to prevent OM w/ HD chemo ± TBI for HCT
   - No guideline for other natural agents d/t conflicting evidence

Vitamins A and E
Honey
Aloe Vera
Chamomile
Kamillosan
Chinese herbals
Indigowood root

Manuka/kanuka oils
Oral gel wafers
Rhodiola algida
Glutamine in other settings
Traumeel S
Wobe-Mugos E
Summary of MASCC/ISOO Clinical Guidelines

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4. Antimicrobials, coating agents, anesthetics, and analgesics
5. Laser and other light therapy (PBM)
6. Cryotherapy
7. Natural and miscellaneous agents
   - **Favors** zinc to *prevent* OM with chemo +/- RT for oral cancer
   - **Do NOT use** IV Glutamine to *prevent* OM w/ HD chemo ± TBI for HCT
   - No guideline for other natural agents d/t conflicting evidence
   - **Do NOT use** Pilocarpine to *prevent* OM w/ RT +/- TBI in H&NC, or chemo ± TBI for HCT
   - **Do NOT use** Oral Pentoxifylline to *prevent* OM w/ HCT
   - No guideline for other misc. agents d/t inadequate/conflicting evidence
   - Allopurinol
   - Payayor
   - RT timing
   - Bethanechol
   - Midline mucosa-sparing RT blocks
   - Chewing gum
   - Propantheline
   - Tetrachlorodecaoxide
Children are not just little adults
Children and adolescents are more prone to develop OM.
- Incidence rates range from 40% to over 80% among HCT.

OM interventions effective in adults *likely* similar in children **BUT**:
- Different pharmacokinetics and pharmacodynamics
- Varying levels of cooperation
- Different cancers and treatment regimens differ →
  - same OM intervention may not work with different cancer therapies
  - may interfere with anticancer effectiveness.
Risk Factors for OM in Children

- Patient-related
  - Age
  - Type of malignancy or HCT
    - ALL, AML, Lymphoma, Osteosarcoma, HCT
  - Pre-Tx oral health status
  - Prior mucositis
  - Nutritional status

- Treatment-related
Risk Factors for OM in Children

- Patient-related

- Treatment-related

Chemo commonly assoc. w/ OM in children
- Cytarabine
- Doxorubicin
- Etoposide
- Melphalan
- Methotrexate

Regimen
Dose
Route
Frequency of Administration
  Short vs long duration of bolus
Excretion in saliva
  Methotrexate, Etoposide
Absolute Neutrophil Count
Duration of neutropenia
Children are not just little adults
Evidence re: Mucositis in Children Receiving Cancer Therapy or HCT
Building upon Cochrane Collaboration systemic review\(^b\) and the MASCC/ISOO clinical guidelines, with a pediatric focus.

3 interventions showing benefit → **cryotherapy**, **PBM**, and **KGF**
- Did effectiveness differ between adults and children?
- Included RCTs of these 3 agents that included some children

RCTs of any other agent for OM prevention conducted exclusively in children

**Outcomes:**
- severe oral mucositis
- mucositis of any severity
- Mucositis-related pain
- Adverse events associated with OM intervention

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Summary of POGO Recommendations

1. **Cryotherapy** ok to offer cooperative children receiving chemo or HCT with high risk of OM → weak, moderate-quality of evidence

   - 14 RCTs re: cryotherapy; 12 reported benefit.
     - Only 1 included children (youngest was 8 yo)
     - 8 of 14 studies around 5-FU, which is rarely used in children
   - Lacks pediatric-specific evidence, but low risk of harm
   - Inexpensive and relatively easy to administer
   - Most appropriate for use with regimens that have a short infusion time and half-life (ex: Melphalan)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Cryotherapy Events</th>
<th>No Cryotherapy Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<td>Mahood 1991</td>
<td>7</td>
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<td>0.22 [0.01, 4.47] 2007</td>
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<tr>
<td>Gori 2007</td>
<td>29</td>
<td>62</td>
<td>32</td>
<td>60</td>
<td>0.88 [0.61, 1.25] 2007</td>
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<tr>
<td>Sorensen 2008</td>
<td>7</td>
<td>67</td>
<td>21</td>
<td>66</td>
<td>0.33 [0.15, 0.72] 2008</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 364 / 363 100.0% 0.46 [0.30, 0.71]

Total events 64 / 120

Heterogeneity: Tau² = 0.16; Chi² = 14.49, df = 7 (P = 0.04); I² = 52%

Test for overall effect: Z = 3.50 (P = 0.0005)
Summary of POGO Recommendations

2. **PBM (LLLT)** ok to offer cooperative children receiving chemo or HSCT with high risk of OM → *weak, high-quality of evidence*
   - Oberoi\(^c\) systematic review:
     - 18 LLLT studies, only 2 included children
     - LLLT significantly reduced incidence of severe OM (RR 0.37, 95% CI 0.2-0.67, p = 0.001) and **OM-related severe pain** (RR 0.26, 95% CI 0.18-0.37, p < 0.0001)
     - No difference in LLLT by age in the 2 studies that included children (p = 0.90)
     - Lacks pediatric-specific evidence, but low risk of harm
     - Requires specialized equipment and expertise → Feasibility?
     - Ideal treatment parameters and cost-effectiveness unknown
     - Mostly administered intra-orally, but some experience with external

LLLT effective in reducing severe OM in pts receiving cancer Tx or HSCT

3. **KGF** may be offered to children receiving HSCT regimens assoc. with high rate of severe OM → weak, high-quality of evidence
   
   - Lack pediatric-specific efficacy and toxicity, but high value based on adult evidence
   - Theoretical concern that young children have increase risk of adverse effects related to *mucosal thickening* and *lack of long-term data* in pediatric cancers

KGF significantly **reduced severe OM** in the 8 studies reporting this outcome. **BUT** the 1 study w/ children = allo-HSCT, didn’t report ped-specific results.
High risk of mucositis

Child can comply with both cryotherapy and LLLT (and LLLT available)
- Chemotherapy amenable to cryotherapy
  - Consider cryotherapy and/or LLLT
- Chemotherapy not amenable to cryotherapy
  - Consider LLLT

Child can comply with LLLT but not cryotherapy (and LLLT available)
- Consider LLLT

Child can comply with cryotherapy but not LLLT (or LLLT is not available)
- Chemotherapy amenable to cryotherapy
  - Consider cryotherapy
- Chemotherapy not amenable to cryotherapy and child is undergoing HSCT with high risk of severe mucositis
  - Consider KGF, if available, and if prevention of severe mucositis outweighs risks and costs

Child cannot comply with either cryotherapy or LLLT (or LLLT is not available) and child is undergoing HSCT with high risk of severe mucositis
- Consider KGF, if available, and if prevention of severe mucositis outweighs risks and costs
Fundamental Principles of Pediatric Pain Management
Perception and Reaction to Pain is Individualized

Physiologic  Developmental  Psychosocial
Environmental  Situation  Cultural
Behavioral  Contextual

“Pain is whatever the experiencing person says it is, existing whenever the experiencing person says it does” (McCaffery, 1999)
5 Steps to Ensuring Effective Pain Management

1. History
2. Assessment
3. Nonpharmacologic Interventions
4. Pharmacologic Interventions
5. Reassessment
# Variables Used to Assess Pain in Children

- **Physiologic**
  - Heart rate
  - Oxygen saturation
  - Blood pressure
  - Tonicity
  - Respiratory rate

- **Behavioral**
  - Consolability
  - Regressive behaviors
  - Activity level
  - Disinterest in play
  - Posture/position
  - Disinterest in self

- **Subjective**
  - Child
  - Parent
  - Clinicians
Instruments to Assess Pain in Children

✧ Neonates
   N-PASS, NIPS

✧ Toddlers/non-verbal children
   FLACC

✧ Early school-age children
   Faces pain scale

✧ Teenagers
   Numeric pain scale
## Neonatal Infant Pain Scale (NIPS)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Finding</th>
<th>Points</th>
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</thead>
<tbody>
<tr>
<td>Facial Expression</td>
<td>Relaxed</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Grimaced</td>
<td>1</td>
</tr>
<tr>
<td>Cry</td>
<td>No cry</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Whimper</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Vigorous cry</td>
<td>2</td>
</tr>
<tr>
<td>Breathing</td>
<td>Relaxed</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Altered</td>
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</tr>
<tr>
<td>Arms</td>
<td>Relaxed</td>
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</tr>
<tr>
<td></td>
<td>Flexed/extendend</td>
<td>1</td>
</tr>
<tr>
<td>Legs</td>
<td>Relaxed</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Flexed/extendend</td>
<td>1</td>
</tr>
<tr>
<td>State of arousal</td>
<td>Sleeping/awake</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Fussy</td>
<td>1</td>
</tr>
</tbody>
</table>
Faces Scale: > 6 years

Wong-Baker Faces

0
NO HURT

1
HURTS A LITTLE BIT

2
HURTS A LITTLE MORE

3
HURTS EVEN MORE

4
HURTS A WHOLE LOT

5
HURTS WORST

Faces Pain Scale – Revised 2001
Faces Pain Scale - Revised

This scale is intended to measure how children feel INSIDE, not how their face looks

“These faces show how much something can hurt. This face (point to left-most face) shows no pain. The faces show more and more pain (point to each from left to right) up to this one (point to right most). It shows very much pain. Point to the face that shows how much you hurt (right now).”
Assessing mucositis pain in children

Children’s International Mucositis Evaluation Scale (ChIMES)

## Pain

1. Which of these faces best describes how much pain your child feels in their mouth or throat today? Circle one.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No hurt</td>
<td>Hurts a little bit</td>
<td>Hurts a little more</td>
<td>Hurts even more</td>
<td>Hurts a whole lot</td>
<td>Hurts worst</td>
</tr>
</tbody>
</table>

## Swallow

2. Which of these faces shows how hard it is for your child to SWALLOW their saliva/spit today because of mouth or throat pain? Circle one.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not hard</td>
<td>Little bit hard</td>
<td>Little more hard</td>
<td>Even harder</td>
<td>Very hard</td>
<td>Can't swallow</td>
</tr>
</tbody>
</table>

3. Which of these faces shows how hard it is for your child to EAT today because of mouth or throat pain? Circle one.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not hard</td>
<td>Little bit hard</td>
<td>Little more hard</td>
<td>Even harder</td>
<td>Very hard</td>
<td>Can't eat</td>
</tr>
</tbody>
</table>

4. Which of these faces shows how hard it is for your child to DRINK today because of mouth or throat pain? Circle one.

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not hard</td>
<td>Little bit hard</td>
<td>Little more hard</td>
<td>Even harder</td>
<td>Very hard</td>
<td>Can't drink</td>
</tr>
</tbody>
</table>

## Pain Medication

5. Has your child taken medicine for any kind of pain today?

- [ ] Yes
- [ ] No

If yes, did your child need the medicine because they had mouth or throat pain?

- [ ] Yes
- [ ] No

## Appearance

6. Please look in your child's mouth. Can you see any mouth sores (ulcers)?

- [ ] Yes
- [ ] No
- [ ] Can't tell

## Use of pain med

### Child

- <12 Parent
- 8-12 Both
- >12 Self (child)

### Reporter

- Parent
- Both
- Self (child)

### Visual assessment
1. Which of these faces best describes how much pain you feel in your mouth or throat today? Tap one.

0 No hurt 1 Hurts a little bit 2 Hurts a little more 3 Hurts a whole lot 4 Hurts worst

2. Which of these faces shows how hard it is for you to SWALLOW your saliva/spit today because of mouth or throat pain? Tap one.

0 No hurt 1 Hurts a little bit 2 Hurts a little more 3 Hurts a whole lot 4 Can’t swallow

3. Which of these faces shows how hard it is for you to EAT today because of mouth or throat pain? Tap one.

0 No hurt 1 Hurts a little bit 2 Hurts a little more 3 Hurts a whole lot 4 Can't eat

4. Which of these faces shows how hard it is for you to DRINK today because of mouth or throat pain? Tap one.

0 No hurt 1 Hurts a little bit 2 Hurts a little more 3 Hurts a whole lot 4 Can’t drink

5. Have you taken any medicine for any kind of pain today? □ Yes □ No

6. Please ask an adult to look in your mouth. Can he or she see any mouth sores in your mouth today?

□ Yes □ No □ I can’t tell
Common Non-Pharmacologic Strategies

<table>
<thead>
<tr>
<th>Comfort Measures</th>
<th>Guided Imagery</th>
</tr>
</thead>
<tbody>
<tr>
<td>- pacifier, swaddling, sucrose pacifiers</td>
<td>- music, emotive imagery, special place</td>
</tr>
<tr>
<td>Distraction</td>
<td>Progressive Muscle Relaxation</td>
</tr>
<tr>
<td>- reading, bubbles, video games, music</td>
<td></td>
</tr>
<tr>
<td>Breathing Techniques</td>
<td>Self-hypnosis/self-regulation activities</td>
</tr>
<tr>
<td>- patterned, shallow, rhythmic</td>
<td></td>
</tr>
</tbody>
</table>
Non-pharmacological Approaches

TODDLERS
✧ Complementary
✧ Massage
✧ Warm/cool compresses
✧ Aromatherapy
✧ Cognitive behavioral
✧ Story telling
✧ Blowing bubbles
✧ Toys
✧ Distraction
✧ Art and music therapy

PRESCHOOLERS
✧ Complementary
✧ Massage
✧ Warm/cool compresses
✧ Aromatherapy
✧ Reiki
✧ Emotive imagery
✧ Cognitive behavioral
✧ Distraction
✧ Art and music therapy
✧ Favorite toy to hold

Non-pharmacological Approaches

**SCHOOL AGE & ADOLESCENTS**

✧ Complementary
  ✧ Yoga
  ✧ Massage
  ✧ Warm/cool compresses
  ✧ Aromatherapy
  ✧ Reiki
  ✧ Emotive imagery

✧ Cognitive behavioral
  ✧ Biofeedback
  ✧ Guided imagery
  ✧ Progressive relaxation
  ✧ Journal
  ✧ Art & Music Therapy

Pharmacologic Treatment of Pain in Children

- Local Anesthetics and Topical Analgesics
- Acetaminophen and NSAIDS
- Opioids
- Combination Medications
Topical Agents for Mucositis Pain in Children

✧ Bland rinses
  ✧ Saline
  ✧ Hydrogen peroxide
✧ Viscous lidocaine
✧ Single dose of lidocaine 2% (5 ml swish and spit)
✧ Benzydamine topical rinse
✧ Lip balms, salves, and other coating agents

✧ No significant evidence to support use of mouthwashes often called “magic mouthwash”
A 2-step approach vs the 3-step ladder

It is recommended to use the analgesic treatment in two steps according to the child’s level of pain severity

Step 1: mild pain
• Acetaminophen and NSAIDS
  ± non-opioid ± adjuvant

Step 2: moderate – severe pain
• Opioid analgesics ± non-opioid ± adjuvant
General Principles of Opioid Management

- Keep it simple
- Avoid mixed preparations
- Steady pain control works best
- Reassess and adjust as needed
- Anticipate, prevent, treat toxicities

<table>
<thead>
<tr>
<th>Constipation</th>
<th>Itching</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/Vomiting</td>
<td>Confusion</td>
</tr>
<tr>
<td>Myoclonus</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td></td>
</tr>
</tbody>
</table>
Intravenous administration of opioids

✦ Most common routes of administration
  ✦ Intravenous
  ✦ Subcutaneous (far less common)
  ✦ Patient-controlled analgesia used for older kids
    ✦ Emerging use of PARENT-controlled analgesia

✦ Most common opioids utilized
  ✦ Morphine
  ✦ Hydromorphone (Dilaudid)
IV Morphine: Start Low and Work Up

**Infants ≤6 months**
- 0.025 to 0.03 mg/kg/dose every 2 to 4 hours

**Infants >6 months, Children, and Adolescents**

Patient weight <50 kg:
- Opioid naïve initial: **0.05 – 0.1 mg/kg/dose** every 2 to 4 hours
- Opioid tolerant: **0.1 to 0.2 mg/kg/dose** every 2 to 4 hours

Patient weight ≥50 kg:
- Initial: 2 to 5 mg every 2 to 4 hours

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Max Dose of IV Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td>2 mg/dose</td>
</tr>
<tr>
<td>Children 1-6 yo</td>
<td>4 mg/dose</td>
</tr>
<tr>
<td>Children 7-12 yo</td>
<td>8 mg/dose</td>
</tr>
<tr>
<td>Adolescent</td>
<td>10 mg/dose</td>
</tr>
</tbody>
</table>
**IV Morphine Administration**

1. **Start with an IV dose (e.g., 2 mg IV morphine)**
   - prn for intermittent pain
   - scheduled for steady or frequent pain

2. **Determine how many doses needed over 24 hours**
   - 12 doses x 2 mg/dose = 24 mg

3. **Give that dose continuously:** 1 mg/hr

4. **Add prn dosing:** 1 mg prn (usually every 15 minutes)

5. **Monitor, Reassess frequently, adjust as needed**
“With the current lack of evidence-based guidance in this area, and the existing large variations in daily practice, a CPG could be pivotal to improve pain outcomes and quality of life. We therefore initiated the development of a comprehensive CPG regarding pain in children with cancer.”
FIGURE 2  Flowchart of the study search and selection regarding clinical questions on the management of pain in children with cancer
89 clinical questions identified

22 after voting

7 studies Identified in 2b group = toxicity-related pain

Identified 5 studies on mucositis pain management in children with cancer


Brief Review of Recent RCT and CTs about OM in Children Receiving Cancer Therapy or HCT
Photobiomodulation Update

- LLLT (or PBM) recommended both MASCC and POGO
- Ped LLLT reviewed by He et al (2018, incl. 2015 pub)


- Recently, several new RCTs in children supporting PBM
  - Prevention of OM in children:
    - reduces OM frequency, severity, and duration
  - Treatment of OM in children:
    - Reduces OM severity, incidence and overall pain, and use of analgesia

Photobiomodulation Update: Treatment

Photobiomodulation Update


14 studies reviewed, most included in 2017 He article, except for this Russian one.

PBM to **TREAT** Mucositis Pain in Children

Ages 7-15 yo (3-18 yo eligible)
Multicenter RCT

Primary outcome:
- severity of OM day +7

Secondary outcomes:
- OM days +4 and 11
- pain
- decreased analgesia use
- adverse events

Diode laser treated on Days +1 → +4
- 660 and 970 nm-combined wavelength
- 3.2 W peak power
- 320 mW/cm² irradiance
- 36.8 J/cm²
- 50% frequency
- 9 areas of oral cavity treated
- 2 consecutive 2-3 min treatments

PBM to **TREAT** Mucositis Pain in Children


<table>
<thead>
<tr>
<th>Study results</th>
<th>Laser therapy (n = 51)</th>
<th>Sham therapy (n = 50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>OM grade at day +4, number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>7 (14%)</td>
<td>12 (24%)</td>
<td>0.19</td>
</tr>
<tr>
<td>Grade 3</td>
<td>16 (31%)</td>
<td>19 (38%)</td>
<td></td>
</tr>
<tr>
<td>Grade &lt; 3</td>
<td>28 (55%)</td>
<td>19 (38%)</td>
<td></td>
</tr>
<tr>
<td>OM grade at day +7, number (%)</td>
<td>(n = 49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (2.0%)</td>
<td>8 (16%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (4.1%)</td>
<td>6 (12%)</td>
<td></td>
</tr>
<tr>
<td>Grade &lt; 3</td>
<td>46 (94%)</td>
<td>36 (72%)</td>
<td></td>
</tr>
<tr>
<td>OM grade at day +11, number (%)</td>
<td>(n = 49)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>5 (10%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Grade 3</td>
<td>1 (2.1%)</td>
<td>5 (10%)</td>
<td></td>
</tr>
<tr>
<td>Grade &lt; 3</td>
<td>47 (98%)</td>
<td>40 (80%)</td>
<td></td>
</tr>
<tr>
<td>Self-reported pain score at day +4, median (IQR)</td>
<td>4 (2–6)</td>
<td>5 (3–7)</td>
<td>0.07</td>
</tr>
<tr>
<td>Self-reported pain score at day +7, median (IQR)</td>
<td>1 (0–3)</td>
<td>2.5 (1–5)</td>
<td>0.006</td>
</tr>
<tr>
<td>Self-reported pain score at day +11, median (IQR)</td>
<td>0 (0–1)</td>
<td>1 (0–3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Analgesic use at day +7, number (%)</td>
<td></td>
<td></td>
<td>0.60</td>
</tr>
<tr>
<td>Parenteral</td>
<td>15 (31%)</td>
<td>18 (36%)</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>5 (10%)</td>
<td>8 (16%)</td>
<td></td>
</tr>
<tr>
<td>Topical</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>4 (8.2%)</td>
<td>5 (10%)</td>
<td></td>
</tr>
<tr>
<td>No use</td>
<td>25 (51%)</td>
<td>19 (38%)</td>
<td></td>
</tr>
<tr>
<td>Neutrophil count at day +4, median (IQR)</td>
<td>100 (0–800)</td>
<td>104 (0–580)</td>
<td>0.98</td>
</tr>
<tr>
<td>Neutrophil count at day +7, median (IQR)</td>
<td>770 (100–1938)</td>
<td>917 (50–2100)</td>
<td>0.79</td>
</tr>
<tr>
<td>Neutrophil count at day +11, median (IQR)</td>
<td>1456 (503–4158)</td>
<td>1380 (275–2875)</td>
<td>0.32</td>
</tr>
<tr>
<td>Admission due to isolated OM (n = 48) 6/48 (13%)</td>
<td>8 / 50 (16%)</td>
<td></td>
<td>0.62</td>
</tr>
</tbody>
</table>
Photobiomodulation Update: Treatment High-Power Laser Therapy (Pilot Clinical Trial)

- 16 ped HCT randomize, blind CT → HPLT or Sham
  - HPLT = 970 nm, 3.2 W (50%), 35-60,000 Hz, 240 s
  - Treatments daily x 4 from first OM Sx
- Outcomes at days 0, 3, 7 and 11
  - Severity and duration of OM → WHO OM grading scale
  - OM-associated pain → Visual Analogue Scale (pain)

Photobiomodulation Update

• Intraoral vs extraoral?
• Optimal dosing and delivery?
• Other new PBM modalities?

1. Anna N. Yaroslavsky, Nathaniel S. Treister et al, "A Monte Carlo simulation of the dosimetry of extraorally delivered photobiomodulation therapy (Conference Presentation)," Proc. SPIE 10477, Mechanisms of Photobiomodulation Therapy XIII, 104770H (14 March 2018);
Photobiomodulation (PBM) Update

Intraoral

- Multiple RCTs and meta-analyses showing effective
  - Adults and children
  - Prevention and for pain
- More complex procedure
  - Spots vs scanning
- Treatment parameters defined, but not optimal & no dose response
  - Dose in children?

Extraoral

- Simpler application, larger treatment
- LED arrays allow larger surface to be treated with a single exposure
- More comfortable for patient
  - especially children
- Requires unique device/treatment parameters d/t skin/tissue attenuation
  - Median-centered treatment plan approach?

Anna N. Yaroslavsky, Nathaniel S. Treister et al, "A Monte Carlo simulation of the dosimetry of extraorally delivered photobiomodulation therapy (Conference Presentation)," Proc. SPIE 10477, Mechanisms of Photobiomodulation Therapy XIII, 104770H (14 March 2018);
Use of KGF for Children Receiving HCT

- **RCT**
- **prevention**
- Ages 7 – 16 yo
- ALL → HCT
- KGF daily x 3, twice
  - 60 mcg/kg/day
  - 3 days prior to conditioning, then
  - Days 0, +1 and +2

**Outcomes:**
- WHO oral-toxicity scale
- self-reported Oral Mucositis Daily Questionnaire

Use of KGF for Children Receiving HCT

Use of KGF for Children Receiving HCT

**Table III. Efficacy of palifermin in the control and palifermin groups.**

<table>
<thead>
<tr>
<th></th>
<th>Palifermin group (n = 27)</th>
<th>Control group (n = 27)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of ulcerative OM, n (%)</td>
<td>12 (48)</td>
<td>18 (72)</td>
<td>0.081</td>
</tr>
<tr>
<td>Duration of ulcerative OM days, mean (SD)</td>
<td>6 (1.2)</td>
<td>15 (1.6)</td>
<td>0.027</td>
</tr>
<tr>
<td>Incidence of severe OM, n (%)</td>
<td>4 (16)</td>
<td>7 (28)</td>
<td>0.124</td>
</tr>
<tr>
<td>Duration of severe OM days, median (range)</td>
<td>3.0 (0–21)</td>
<td>8.0 (0–26)</td>
<td>0.04</td>
</tr>
<tr>
<td>AUC for Patients-reported MTS, mean (SD)</td>
<td>30 (41)</td>
<td>45 (33)</td>
<td>0.06</td>
</tr>
<tr>
<td>Mean grading of mucositis</td>
<td>1.65</td>
<td>2.33</td>
<td>0.033</td>
</tr>
</tbody>
</table>

AUC, area under the curve; MTS, mouth and throat soreness; OM, oral mucositis; SD, standard deviation.

**Table IV. Efficacy of palifermin in the control and palifermin groups for patient-reported outcomes.**

<table>
<thead>
<tr>
<th>Scale</th>
<th>Palifermin group (n = 27)</th>
<th>Control group (n = 27)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleeping, mean (SD)</td>
<td>0–5</td>
<td>1 (0.6)</td>
<td>3 (1.1)</td>
</tr>
<tr>
<td>Swallowing, mean (SD)</td>
<td>0–5</td>
<td>1 (0.5)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Drinking, mean (SD)</td>
<td>0–5</td>
<td>1 (0.3)</td>
<td>4 (1.1)</td>
</tr>
<tr>
<td>Eating, mean (SD)</td>
<td>0–5</td>
<td>2 (0.4)</td>
<td>3 (3.3)</td>
</tr>
<tr>
<td>Talking, mean (SD)</td>
<td>0–5</td>
<td>0 (0.2)</td>
<td>3 (0.2)</td>
</tr>
</tbody>
</table>

Scale: 0 = Not limited, 5 = Unable to do.

- Decrease duration of severe OM
- Less mucosal pain
- Decreased use of narcotics
- Improved ability to
  - Sleep
  - Swallow
  - Drink
  - Eat
  - Talk
  - General Quality of life

Thank You!

Email: Lauren_Bruckner@URMC.Rochester.EDU
1. Basic oral care
   • **Favors** oral care protocols (toothbrushing, flossing, daily mouth rinse) for all to **prevent** OM
   • **Do NOT use** Chlorhexidine (at least not for H&NRT) to **prevent** OM
   • No guideline about which **mouth rinse** is best, but use of anything regularly better than none

2. Growth factors and cytokines
   • **Recommends** KGF (Palifermin) to **prevent** OM in HD chemo + TBI auto-HCT for heme Cancers
   • **Did NOT support** GM-CSF to **prevent** OM in HD chemo for auto- or allo- HCT
   • No guidelines for many others

3. Anti-inflammatory agents
   • **Recommends** Benzydamine mouthwash to **prevent** OM in RT for H&NC (< 50 Gy) w/o chemo
     • But no guideline for >50 Gy
   • **Do NOT use** Misoprostil MW to **prevent** OM in RT for H&NC
     • No guideline about **Amifostine** to **prevent** OM nor others

4. Antimicrobials, coating agents, anesthetics, and analgesics
   • **Recommends** Morphine PCA; **Favors** Fentanyl patch, Morphine and Doxepine MW to **treat** OM pain
   • **Do NOT use** Antimicrobial lozenge & pastes (PTA, BCoG) or Iseganan MW to **prevent** OM w/ RT for H&NC
   • **Did NOT support** Sucralfate to **prevent or treat** OM w/ chemo or RT for H&NC
   • No guideline possible for any anesthetic nor many other agents

5. Laser and other light therapy (PBM)
   • **Recommends** LLLT to **prevent** OM in HCT and **Favors** LLLT to **prevent** OM in RT alone for H&NC
   • No guideline for LLLT in other settings or for **other emerging light Tx** to prevent or treat OM

6. Cryotherapy
   • **Recommends** cryotherapy to **prevent** OM w/ 5-FU; **Favors** it to **prevent** OM w/ HD Melphalan in HCT +/- TBI
   • No guideline for **cryotherapy** in other settings due to inadequate evidence

7. Natural and miscellaneous agents
   • **Favors** zinc to **prevent** OM with chemo +/- RT for oral cancer
   • **Do NOT use** IV Glutamine, Pilocarpine, or Pentoxyfyline to **prevent** OM w/ HD chemo ± TBI for HCT
   • **Do NOT use** Pilocarpine to **prevent** OM w/ RT +/- TBI in H&NC
   • No guideline for many other natural and miscellaneous agents d/t inadequate/conflicting evidence