Oral Mucositis in the BMT Patient

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Mucositis

- Mucosal changes characterized by
  - erythema
  - inflammation
  - ulcers
- Involves the
  - lining of the mouth
  - pharynx
  - esophagus
  - gastrointestinal tract

Incidence

- General oncology:
  - True incidence is unknown due to under-reporting
  - Estimated to be 20-40%
- BMT:
  - 60-85% depending on conditioning
  - Typically higher in pediatric populations compared with adult

Risk factors

- TBI-containing regimens
- Type of chemotherapy
  - Melphalan
  - Cyclophosphamide
  - Busulfan
  - *Methotrexate (MTX)*
    - Leucovorin rescue can begin 12–24 hours after administration of MTX
  - Etoposide
  - Thiotepa
  - Cytarabine


Risk factors

- Type of transplant
  - allogeneic
  - autologous
- Age (young or old)
- Female gender
- History of
  - Cigarette use
  - Prior cancer treatment

Villa, A. & Sonis, S. (2015). Curr Opin Oncol 27(3);
Onset and duration
- Symptoms appear 2-10 days after radiation and/or chemotherapy
- Resolution usually coincides with engraftment
  - Neutrophils and phagocytes assist in healing (approximately 10-21 days post transplant)

Historical theory
- Chemo-radiotherapy affects rapidly dividing cells of the oral mucosa

Current theory
Complex chain reaction leading to sub-mucosa and fibroblast damage

Phase 1 (initiation)
- Occurs immediately after radiation or chemotherapy
- Involves both DNA and non-DNA damage to the cells, tissues and blood vessels
- Generation of reactive oxygen species
- The mucosa will appear normal

Phase 2 (signaling)
- Most damage occurs during this phase
- Production of
  - Proinflammatory cytokines TNF-alpha, IL-1, IL-6
  - Nitric oxide
  - Matrix metalloproteinases
- Damage-associated pattern molecules (CRAMPs)
- Patient remains asymptomatic

Phase 3 (amplification)
- Proinflammatory cytokines damage tissues and create a positive feedback loop that amplifies the damage
- Both the epithelium and the sub-mucosa are involved
- Apoptosis occurs
- Some erythema and early ulceration may be seen

Positive Feedback Loop

Chemoradiotherapy

- Nuclear factor-κB (NFκB) up-regulates pro-inflammatory cytokines
  - TNF-α, IL-1β, and IL-6
- Tissue injury and cell death
- Stimulate more production of TNF-α, IL-1β, and IL-6

Phase 4 (ulceration)
- Compromise of mucosal integrity
- Development of pseudomembranes
  - Filled with bacteria which release toxins and lead to further cellular injury from mononuclear cells which produce and release proinflammatory cytokines
- Bleeding
- Exposed nerve endings cause severe pain

Phase 5 (healing)
- Tissues may appear “normal,” but the oral mucosa is still susceptible to injury for up to one year post transplant
- Healed epithelial layer is thinner than normal

Example
- Raised borders around the tongue and inside of the lips are full thickness ulcers
- The pseudomembrane is made of dead cells, fibrin and bacteria

Example
- Pseudomembrane may slough off, exposing raw tissue, with full thickness ulceration
- The dorsal surface of the tongue and lips are usually spared

Mucositis grading scales
- Provide a consistent method of assessing documenting mucositis
- The absence of a universally agreed upon grading or scoring scale has made it difficult to compare
  - toxicity of regimens
  - efficacy of prophylaxis and treatment measures
- Several scales are in use
Oral Mucositis Assessment Scale

Individually Scores and Averages 8 Regions of the Oral Cavity

- **ERYTHEMA**
  - 0 = None
  - 1 = Mild / Moderate
  - 2 = Severe (mucosa the color of fresh blood)

- Ulcerations / Pseudo membranous lesions
  - 0 = no lesions
  - 1 = cumulative surface area of lesions in a single site < 1 cm²
  - 2 = cumulative surface area of lesions in a single site ≥ 1 cm² but ≤ 3 cm²
  - 3 = cumulative surface area of lesions in a single site > 3 cm²


NCI and WHO scales

<table>
<thead>
<tr>
<th>NCI Grading Scale</th>
<th>WHO Grading Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>None</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Painful ulcers, erythema, or mild soreness without ulcer</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Painful erythema, edema, or ulcers, but eating or swallowing possible</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Painful erythema, edema, or ulcers requiring IV hydration</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Severe ulceration or requiring parental or enteral nutrition support or prophylactic intubation</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to toxicity</td>
</tr>
</tbody>
</table>

| Grade 0 | None |
| Grade 1 | Oral ulcers, wounds |
| Grade 2 | Oral ulcers, patients can swallow solid diet |
| Grade 3 | Oral ulcers, liquid diet |
| Grade 4 | Oral alimentation is not possible |

Signs and Symptoms

- Initial complaints may include xerostomia and/or throat pain
- Parotitis if receiving TBI
- Progression to copious stringy, “ropey” secretions “resembling rubber cement”
- Oral cavity may be erythematous with white pseudomembranes (plaques)
- Can cause severe pain requiring narcotic analgesia, described as the worst part of transplant

A patient’s perspective


Implications

- Difficulty speaking
- Difficulty eating and swallowing
  - Often cannot take oral medications, including analgesics
  - May need to be admitted for IV medications
- Potential airway compromise
  - May require intubation for airway protection or patency

A patient’s perspective

Psychosocial:
- Increased mood disturbances
- Increased depression and anger scores
- Fear of choking and/or suffocation
Increased risk of

- Infection
  - Bacterial (E. coli, pseudomonas, Klebsiella, Stomatia)
  - Fungal (Candida, Aspergilus)
  - Viral (Herpes Simplex, Cytomegalovirus)
  - Brown & Wingard study: Patients with ulcerative mucositis were 3x more likely to develop alpha hemolytic strep bacteremia
- Aspiration pneumonia

Implications

- Increased length of hospitalization
- Sonis study of 92 HSCT patients: each 1 point increase in the OMAS score corresponded to
  - A 3.9-fold increase in 100-day mortality risk
  - $25,400 in added hospital charges
  - 5.8 additional days of narcotics
  - 1.9 additional days of TPN
  - 2 additional febrile days

Prevention and treatment

- No "gold standard" exists for prevention and treatment of oral mucositis

General preventative measures

- Pre-transplant dental evaluation to assess for periodontal disease
  - Have needed dental work performed prior to conditioning
  - Remove braces
- Medications
  - Acyclovir to prevent HSV reactivation in HSV+ patients (reactivation higher in patients with mucositis)
  - Fluconazole to inhibit fungal growth

2014 MASCC* Evidence Based Guidelines (BMT)

- Recommendations: (strong evidence)
  - Palifermin
  - Low Level Laser Therapy
  - Cryotherapy for Melphalan
- Suggestions: (less evidence)
  - Oral hygiene

Palifermin (Kepivance™)

- A recombinant protein that mimics the activity of endogenous keratinocyte growth factor (KGF)
- Binds to the KGF receptor on the cell surface and stimulates epithelial cell proliferation, differentiation, and migration

*Multinational Association of Supportive Care in Cancer 2014
Palifermin

- Indicated as supportive care for preparative regimens predicted to result in ≥ WHO Grade 3 mucositis in the majority of patients
- FHCRC/SCCA use limited to autologous CY-VP-TBI
- Not effective in decreasing the incidence of severe mucositis in allogeneic BMT, or with Melphalan
- Expensive
- Rash is most commonly reported side effect

Cryotherapy

- Hold ice 30 minutes prior to, during and after chemotherapy
  - Mori (2006) (n = 17)
  - Liddle (2006) (n = 40)
  - Gni (2007) (n = 17)
  - Svanberg (2010) (n = 88)
  - Vokurka (2011) (n = 128)
  - Vokura (2012) (n = 142)
  - Salvador (2012) (n = 46)
  - Askari (2016) (n = 23)
  - Marchesi (2016) (n = 72)

Low Level Laser Therapy

- Chor (2009)
- Obero (2014)
- Silva (2014)
- Ferreira (2015)
- Migliorati (2013)
  - Review of 24 RCTs
  - Effective in reducing pain for BMT patients
  - Effective for the prevention of severe oral mucositis and intense pain
Low Level Laser Therapy

- Has an anti-inflammatory effect and promotes wound healing
- Regulation of IL-1β, TNF, and IL-6
- Stimulates the production of collagen, serotonin, and cortisol
- Promotes the activation of local microcirculation and increases fibroblastic activity
- Direct nerve stimulation with endorphin production


Low Level Laser Therapy

Autologous HSCT receiving Melphalan 200mg/m² total

<table>
<thead>
<tr>
<th>Mucositis Grade</th>
<th>Control n=33</th>
<th>%</th>
<th>LLLT only n=17</th>
<th>%</th>
<th>Cryo + LLLT n=54</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>0.00%</td>
<td>8</td>
<td>47.1%</td>
<td>50</td>
<td>92.6%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>7</td>
<td>21.2%</td>
<td>8</td>
<td>47.1%</td>
<td>4</td>
<td>7.4%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>17</td>
<td>51.5%</td>
<td>1</td>
<td>5.9%</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Grade 4</td>
<td>9</td>
<td>27.3%</td>
<td>0</td>
<td>0.0%</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

de-Paula Eduardo, F. et al. (2014). Hematological Oncology, February.

Oral care for prevention

- No single regimen has been proven superior
- Insufficient studies

Oral care for prevention

  - Pediatric oncology patients (n=42)
  - No oral care vs. oral care regimen
  - 60% reduction in ulcerative mucositis during neutropenia in the oral care group

Cheng KKF et al. European J of Cancer 2001

Near Infrared LED

- Safe and less expensive than LLLT
- Easier to use:
  - Compact size
  - Less weight
  - Cover a wider area
- 1 randomized, double-blinded, placebo-controlled study (n = 80)*
- 1 Historical control prospective study (n = 32)**

**Chamomilla recutita**

- Phase II RCT
- Chamomilla recutita mouthwash
- N = 40 allogeneic patients
- Statistically significant decrease in:
  - Incidence
  - Intensity
  - Duration

**EPO Mouthwash**

- Randomized controlled study (n = 80 autologous BMT patients)
- NHL, HD and Myeloma

<table>
<thead>
<tr>
<th>Variables</th>
<th>EPO group (n=40)</th>
<th>Control group (n=40)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral mucositis incidence</td>
<td>27.5%</td>
<td>77.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Grade 2-4 incidence</td>
<td>25.0%</td>
<td>57.5%</td>
<td>0.003</td>
</tr>
<tr>
<td>Grade 3-4 incidence</td>
<td>10.0%</td>
<td>25.0%</td>
<td>0.077</td>
</tr>
<tr>
<td>Maximum WHO Score</td>
<td>0.60±1.06</td>
<td>1.67±1.27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration (days)</td>
<td>1.92±3.42</td>
<td>5.42±3.86</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Limitations:**
- Small study
- 4 arm design
- Included AA, AML, ALL patients
- 63% male
- Mean age 36

**EPO Mouthwash**

- Limitations:
  - Conditioning regimens included
  - Melphalan
  - Carboplatin
  - Etoposide
  - Cytarabine
  - Heterogeneous diseases

**Hosseinjani, H. 2017, Hematol Oncol 2017; 35: 106–112**

**Not Recommended**

- Antimicrobial mouthwash
- Chlorhexidine (for symptom management)
- Sucralfate

**Oral Care**

- Magic mouthwash (Lidocaine, diphenhydramine, magnesium/aluminum oxide)
  - No proof of superiority when compared to NS
  - May cause residue buildup on mucous membranes
  - Can contribute to tooth decay
  - Potential source of infection due to container contamination

**MASCC 2014 oral mucositis guidelines**
Oral Care

- **NS Rinses**
  - Frequency more important than solution
  - ¾ tsp. per quart of water = 0.9% saline
  - Sodium bicarbonate can be added
  - Sterile NS not required

http://www.cancer.gov/cancertopics/pdq/supportivecare/oralcomplications/HealthProfessional/page5#_85_toc

Nursing assessment

- **Color**
- **Presence of:**
  - Lesions
  - Bleeding
  - Swelling
  - Secretions
  - Airway compromise
  - Pain

Nursing management

- **Frequent oral care (q 1-2 hours)**
  - Rinsing (iced or room-temperature normal saline with or without sodium bicarbonate)
  - Brushing with soft brush
  - Flossing (if no bleeding present)
  - Avoid mouthwash/toothpaste or lemon glycerin swabs
  - Gentle suction (avoid trauma)


Pain control

- **Narcotics**
  - PCA morphine or hydromorphone
  - Investigational use of oral morphine rinses*
- **Topicals**
  - Lidocaine
  - Lanolin for lips (no Vaseline)
- **Rinsing**
  - Saline
  - Ice packs to throat or cheeks

*Cerchetti, 2006; Vayne-Bossert, 2010; Sarvizadeh, 2015

Patient Education

- **Avoid foods that are:**
  - Hot
  - Spicy
  - Have sharp edges (e.g. tortilla chips, pretzels)
  - Salty
- **Also avoid:**
  - Alcohol (mouthwash)
  - Toothpaste with strong flavors
  - Swallowing mucus


Case Study

- 56 year old male with stage IV mantle cell lymphoma
- Past chemotherapy included:
  - 5 cycles of rituximab plus Hyper CVAD
  - cyclophosphamide
  - vincristine
  - doxorubicin
  - dexamethasone
  - With alternating high-dose methotrexate and cytarabine
**Treatment Plan**

- Autologous PBSC transplant
- Conditioning protocol:
  - TBI 1.5Gy BID x 4 days (12Gy)
  - Etoposide 60 mg/kg
  - Cyclophosphamide 100 mg/kg
- Palifermin
  - 60mcg/kg x 6 doses (3 pre/3 post)

**Treatment schema**

**Day -4 (etoposide)**
- Denies oral pain
- No erythema or plaques
- Complains of:
  - Food tasting "like cardboard"
  - Cheeks and tongue feel "thick"
  - "Slime" in throat causing gagging

**Day -2 (cyclophosphamide)**
- Painless Grade 1 oral mucositis with slight redness
- Continues to complain of:
  - Bad taste in mouth
  - "Thick cheeks and tongue"
  - Increased mucous "slime" in throat

**Day 0 (stem cell reinfusion)**
- Denies oral pain
- Grade 1 oral mucositis with increased redness and mild swelling
- Everything "tastes bad"

**Day +1 and +2**
- Reports a "lump in my throat"
- Some difficulty in swallowing oral medications (breaking pills in half)
- Still able to eat soft foods
- Denies oral pain
**Day +3**
- Reports worsening throat pain and increased difficulty swallowing oral medications
- Took acetaminophen at night with poor relief
- Given prescription for Oxycodone 5 mg Q6 hours

**Day +4**
- Severe throat pain (now unable to swallow Oxycodone)
- Grade 2 oral mucositis
- New diffuse rash (presumably due to Palifermin)
- ANC = 0
- Febrile to 39.4
- Admitted to inpatient unit for antibiotics and PCA

**Day +4**
- PCA morphine instituted
  - 1.0 mg/6 minute lockout
  - 26 mg PCA used (by midnight)
  - Rating throat pain “10” (on 0-10 scale) and described as “broken glass”
  - Copious mucous present
- TPN instituted

**Day +5**
- Throat pain “7”
- 88 mg morphine PCA used (in 24 hours)
- Thick mucous
- Grade 3 oral mucositis with white plaques
- Unable to swallow anything

**Day +8**
- Rating throat pain “6-8”
- 96 mg morphine PCA used (in 24 hours)
- No oral bleeding
- Encouraged frequent oral rinses with normal saline
- ANC = .01

**Day +9**
- Pain improving
- 62 mg morphine PCA used (in 24 hours)
- Oral mucosa red; white plaques resolving
- ANC = .00
Day +10
- Pain continues to improve
- 66 mg morphine PCA used (in 24 hours)
- Oral mucosa red
- ANC = .01

Day +11
- Pain dramatically decreased to “mild”
- 37 mg morphine PCA used (in 24 hours)
- Able to swallow oral medications and food
- PCA discontinued
- Started on oxycodone 5 mg Q4 hours PRN
- ANC = .02

Day +12
- Throat pain almost completely resolved
- Oral mucosa healing
- Minimal oxycodone use
- ANC = .03

Day +13
- Grade 1 Oral Mucositis
- Able to eat and drink but appetite poor
- TPN discontinued
- Discharge planned for following day
- ANC = .35

Day +14
- Discharged from hospital with same-day follow-up in Ambulatory Clinic
- Throat pain completely resolved
- ANC = 1.10

Case study summary
- Grade 3 mucositis developed post conditioning, despite NS rinses and Palifermin
- Severe throat pain required 540 mg morphine PCA (over 8 days)
- Oral pain was not reported by patient
- Resolution of mucositis coincided with engraftment
Summary

- Patients report oral mucositis is the “worst” part of transplant
- Good oral care can help reduce symptoms and complications
- Narcotic analgesia is usually required for pain control