Atlantic Provinces Pediatric Hematology/Oncology Network
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Reviewed and approved by specialists at the IWK Health Centre, NS, and the Janeway Children's Health and Rehabilitation Centre, NL

Guidelines for the Prevention and Management of Mucositis in Children Receiving Cancer Therapy

APPHON/ROHPPA supportive care guidelines have been developed by appropriate Atlantic Provinces health professional specialists (physicians, pharmacists, nurses and other health professionals) using evidence-based or best practice references. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for verifying doses and administering medications and care according to their own institutional formularies and policies and acceptable standards of care.

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BACKGROUND:

Mucositis is defined as inflammatory and/or ulcerative lesions of the oral (pharyngeal, laryngeal and esophageal regions) and/or gastrointestinal tract. Infectious disease, immune deficiency and medications can be causative. One of the major causes of mucositis is high dose cancer therapy. Alimentary tract mucositis refers to the expression of mucosal injury across the continuum of oral and gastrointestinal mucosa from the mouth to the anus.

Mucositis can be caused by chemotherapy and/or radiation therapy. These treatments break down the rapidly dividing epithelial cells of the GI tract leading to ulceration and potentially infection. It occurs in up to 40% of patients receiving conventional therapy and as high as 80% of patients receiving high-dose chemotherapy as conditioning for hematopoietic stem cell transplantation and nearly all patients receiving head and neck radiation. Oral mucositis presents as erythema and/or ulceration of the oral mucosa. The pharyngeal, laryngeal, and esophageal mucosas are also at risk for mucositis, particularly in patients undergoing head and neck radiation. It is usually very painful, requiring opioid analgesics, and impairs nutritional intake and quality of life. Gastrointestinal mucositis presents with debilitating symptoms such as pain, nausea/vomiting and diarrhea. Severe mucositis can necessitate a reduction in the chemotherapy dose or a treatment break in radiation, which can negatively influence prognosis. In addition mucositis has a considerable economic impact due to costs associated with symptom management, nutritional support, management of secondary infection, and hospitalization. Mucositis is a highly significant, and sometimes dose-limiting, toxicity of cancer therapy.

The pathogenesis of mucositis is complex. A 5-stage model has been proposed. Reactive oxygen species, second messengers, proinflammatory cytokines and pathways, and metabolic byproducts of colonizing microorganisms are all believed to play a role in amplifying the tissue injury. A large number of diverse interventions have been tested for mucositis but few approved. Therefore, there is a need for evidence-informed clinical practice guidelines for mucositis to guide clinicians on which interventions are truly effective.

Several international groups have recently developed evidence based guidelines for the management of mucositis. The Multinational Association of Supportive Care in Cancer (MASCC), the European Society of Medical Oncology (ESMO), the Children's Cancer and Leukemia Group (CCLG), the Royal College of Nursing Pediatric Oncology Nurses Forum's (PONF) Mouth Care Group and the Children's Oncology Group. These guidelines differ in the recommendations and lack practical application; therefore it was felt by the authors of this guideline that it is important to develop Clinical Practice consensus guidelines based on the recommendations of the various groups to provide guidance for healthcare providers in oral care and management of mucositis in the Atlantic Provinces.

The following agents will not be discussed in this guideline as the evidence for their use is limited or unsupported in children:

Amifostine, allopurinol mouthwash, GM-CSF and GCSF mouthwash, antibiotic pastes, povidine-iodine, pilocarpine, hydrolytic enzymes, prostaglandin E, antifungal lozenges, propathelene, prednisone, glutamine, pentoxifyline, Na-sucrose gel, traumeel, chamomile, bee glue, immunoglobulin, tetrachlorodecaoxide, oral amphotericin B, cephasol, sucralfate, 5-amino-salicylic acid and its related compounds mesalzine and olsalazine.

ORAL CARE MANAGEMENT:

- All children should undergo a dental assessment at the time of cancer diagnosis, if possible before cancer treatment begins.
- If any invasive dental treatment is required, this should be undertaken by either a consultant or specialist pediatric dentist as appropriate. NOTE: avoid invasive dental procedures in patients receiving bisphosphonates.
- All children diagnosed with cancer should be registered with a dentist throughout treatment.
- The dentist in the community should be notified of the cancer diagnosis and arrangements for care during cancer treatment as directed by the IWK hospital dental team.
- Oral hygiene advice should be given to children and parents prior to the start of cancer treatment and this should be provided both verbally and in writing.
- Oral hygiene advice should be given by a designated member of the dental team or, in the absence of a dentally trained individual, a member of the medical or nursing team who has received appropriate training. Advice by the dental team will be regularly reinforced by oncology team members.
- Advice should be to brush at least twice a day for two minutes, with gel fluoride toothpaste. Brushing should occur regardless of whether gums are bleeding or the hematological status. If bleeding gums are spontaneous without tooth brushing then suspect a low platelet count, however, gums that bleed during brushing are most often reflective of poor oral hygiene, biofilm and associated gingivitis. The toothbrush should be for the sole use of the child and changed on a 3 monthly basis, or sooner if bristles become damaged or oral infection occurs. A soft brush with a small head should be used.
- Avoid toothettes to clean the mouth as it can disrupt the oral mucosa.
- For children up to the age of 6 years, parents/caregivers should be instructed on how to brush their child's teeth.
- The tongue should be gently cleaned with a soft toothbrush.
- All children should be advised to use a non-alcohol based mouth wash daily as part of proper oral hygiene especially during the periods of intensive therapy. The authors of this guideline recommend:
    - Chlorhexidine 0.12% MIC (minimum inhibitory concentration): It has activity against anaerobes, facultative anaerobes and yeast.
    - Less than 6 years: 5 mL swab, or swish and spit twice daily
    - 6 years and greater: 10 mL swish and spit twice daily
    - Leave in mouth for at least 1 minute if possible before spitting. May rinse twice over 30 seconds if preferable.
    - If unable to swish may apply with a soft toothbrush or gauze
    - Wait 30 minutes after brushing teeth to use chlorhexidine mouthwash
    - Avoid mouth washes with alcohol as they dry and crack already thinned tissues
    - Note: Paroex does not contain alcohol but Peridex does and should be avoided.
- Daily oral assessments.
- Gloves should be worn by caregivers when performing oral hygiene.

- Additional aids, e.g. flossing, fluoride tablets should only be given when recommended by a member of the dental team.
- All inpatients should have an oral assessment daily (more frequently if clinically indicated).
- An oral assessment tool such as the Oral Assessment Guide (OAG) is useful if recording the status of the oral cavity (Appendix I):
    - The Eilers' Oral Assessment Guide offers a valid, reliable and clinically useful tool for assessing oral status.
    - The OAG comprises 8 categories that reflect oral health. Each category is assessed and given a score of 1-3 (1=normal, 2=not normal but barrier intact and no loss of function, 3=barrier breakdown and function compromised). The minimum score is 8 (healthy oral cavity) and the maximum is 24 (severe mucositis).
    - The staff responsible for the assessment of the oral cavity should be appropriately trained in the use of the OAG.
    - A total OAG score greater than 8 means an increased risk of oral complications
    - Children with an OAG greater than 8 should be assessed to ensure appropriate analgesia is given.

MUCOSITIS MANAGEMENT:

Risk Factors for Mucositis:

- Stem cell transplantation
- Chemotherapy including high dose methotrexate, anthracyclines (especially continuous infusions), etoposide and Cisplatin
- Head and neck radiation
- Abdominal and Pelvic radiation
- Neutropenia
- Poor nutrition
- Reduced ideal body weight
- Poor oral hygiene
- Decreased saliva production for any reason

Mucositis Assessment:

There are 2 widely accepted mucositis classification tools: (1) by the World Health Organization and (2) by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The latter will be endorsed by the authors of this guideline as this is the scale recommended by the Children's Oncology Group and it incorporates the collective measurement of oral symptoms, signs and functional disturbances rather than clinician-based observation. (Appendix II)

Treatment of Mucositis:

- Mouth lesions should be swabbed for fungal culture and viral PCR (Herpes simplex virus). Remember that co-infection of mucositis induced by radiation or chemotherapy is common. Do not attribute mouth sores solely as a treatment related complication.
- Appropriate pain control is recommended and the continuation of good oral hygiene to reduce oral biofilm, as tolerated.

- Topical anesthetics can provide short-term pain relief for oral mucositis on an empiric basis (See Appendix III for a list of mouth rinses and cautions for use).
- Pain associated with mucositis can be severe. Opiates are often required for the control of such pain. Use the analog or faces pain scale to assess level of pain.
- The Guidelines published by the American Society for Parenteral and Enteral Nutrition state that parenteral nutrition should be considered in children who cannot maintain adequate nutritional intake orally or internally for 5 to 7 days.
- Oral cryotherapy (the placement of ice cubes or ice chips in the mouth and continually replenishing fresh ice during the period of cytotoxic treatment, typically 30-60 minutes). This should be offered to cooperative children receiving chemotherapy associated with high rates of mucositis.
- Some groups of patients are more likely to get oral candidiasis than others. Preventative therapy is not recommended for most patients (i.e. those receiving treatment for solid tumors). A decision needs to be made by the clinician on whether to provide treatment to try to prevent oral candidiasis.
    - When choosing an antifungal agent for the prevention and treatment of candidiasis one that is absorbed from the gastrointestinal tract is recommended (ex. fluconazole). **If fluconazole is prescribed it should be held for 24 hours before and after Vincristine.** If bridging is required for candidiasis treatment an alternate systemic antifungal may be used.
      Dose: Fluconazole 6-12 mg/kg/day IV/PO once daily (maximum 400 mg/day)
    - There is no evidence to support the use of nystatin for the prevention or treatment of candidiasis in children treated for cancer. Other antifungals may be required if fluconazole is not tolerated.
- Consideration should be given to the use of saliva stimulants, artificial saliva, chewing sugar free gum (although this can increase diarrhea due to the laxative effect of sorbitol) or frequent sips of water for the relief of dry mouth.
- Acyclovir is recommended for the treatment of herpes simplex virus positive children receiving chemotherapy and/or radiotherapy.
    - Intraoral lesions and lesions on the lip should be treated with oral acyclovir or valacyclovir
    - For moderate to severe cases, or where oral administration not tolerated intravenous acyclovir should be used
    - Mucocutaneous/gingivostomatitis:
        - Acyclovir: Children 15-30 mg/kg/day IV divided q8h or 80 mg/kg/day PO divided in 3-4 doses up to 14 days **Maximum:** PO 800 mg **24h** (200 mg q6h) if mild to moderate and PO 1.6 grams **24h** (400 mg q6h) if severe.
- Consider acyclovir prophylaxis for patients with recurrent herpes: 50 mg/kg/24h PO divided q12-q6h (maximum PO 800 mg/24h OR frequent recurrences 80 mg/kg/24h PO divided q8h (maximum PO 800 mg/dose).
- Either ranitidine or a proton pump inhibitor orally is recommended for prevention of epigastric pain following treatment with dexamethasone/prednisone in induction leukemia and high dose cyclophosphamide and methotrexate.
- Some evidence exists for the use of low-level light therapy in cooperative children receiving chemotherapy with a high rate of mucositis. This is a consideration because this strategy requires specialized equipment and expertise and it is unknown whether it is feasible to deliver this therapy modality in routine clinical practice. Low level light therapy is based on the physiological effects of low-energy light without thermal

generation. The main effect of phototherapy is anti-inflammatory, influence on wound healing and analgesic. It is typically administered intraorally, although there is some experience with external application.

- Palifermin (a recombinant human KGF or keratinocyte growth factor which is an epithelial growth factor; it is a 28 kD heparin-binding member of the family of fibroblast growth factors). Not enough evidence is available currently to recommend the use of this agent for children receiving standard chemotherapy. It has shown some promise in adult trials of patient receiving hematopoietic stem cell transplant.

APPENDIX I

Oral Assessment Guide for Children and Young People (Adapted from Eilers, 1988)

Category	Method of Observation	Rating 1	Rating 2	Rating 3
Voice	Converse with patient, listen to crying	Normal	Deeper or raspy	Difficulty talking or crying or painful
Ability to swallow	Ask patient to swallow	Normal swallow	Some pain on swallowing	Unable to swallow
Lips	Observe and feel tissue	Smooth, pink and moist	Dry or cracked	Ulcerated or bleeding
Saliva	Insert depressor into mouth, touching center of tongue and the floor of the mouth	Watery	Thick or ropy, excess salivation due to teething	Absent
Tongue	Observe appearance of tissue	Pink, moist and papillae present	Coated or loss of papillae with a shiny appearance with or without redness. Fungal infection.	Blistered or cracked
Mucous Membrane	Observe appearance of tissue	Pink and moist	Reddened or coated without ulceration. Fungal infection.	Ulceration with or without bleeding
Gingiva	Gently press tissue	Pink and firm	Oedematous with or without redness, smooth. Oedema due to teething.	Spontaneous bleeding or bleeding with pressure
Teeth (if no teeth, score 1)	Visual – observe appearance of teeth	Clean and no debris	Plaque or debris in localized areas (between teeth)	Plaque or debris generalized along gum line

APPENDIX II

NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03:

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis	• Asymptomatic or mild symptoms • intervention not indicated	• Moderate pain; not interfering with oral intake • modified diet indicated	• Severe pain; interfering with oral intake	• Life-threatening consequences; • urgent intervention indicated	Death

APPENDIX III

Compounded Formulations for Symptomatic Management of Mucositis:

There are numerous “magic” mouthwash preparations. Most contain at least 3 ingredients. These may include an antibiotic to reduce bacterial flora around areas of mucosal breakdown, an antifungal to stop fungal growth, a local anesthetic/pain reliever, an antihistamine for local anesthetic effect, a steroid to reduce inflammation and an antacid to enhance coating of the ingredients in the mouth. Note that nystatin has not been shown to be effective in treating oral fungal infections associated with oral mucositis.

Most formulations are used every 6-8 hours prn with instructions to hold in the mouth for 1-2 minutes then spit out or swallow. Patients should be instructed not to eat or drink for 30 minutes after use.
Caution when recommending mouthwashes with lidocaine especially in very young children with short airways as impairment of glottal function can occur which can result in increased risk of aspiration. Also lidocaine use in very young children increases the chance of chewing and macerating mucosa which increases the chance of infection. The maximal daily dose of lidocaine should not exceed 4mg/kg. In children under 5 a mouthwash with lidocaine should be applied by swab to avoid swallowing.

A) Recipe: Pain relief mouthwash known previously as “magic mouthwash” available at IWK

diphenhydrAMINE 2.5 mg/mL Syrup (50mL)
Lidocaine 2% Viscous Solution (50 mL)
Almagel Plus Suspension (or equivalent) (50 mL)

PROCEDURE:

1. Measure all ingredients.
2. Combine the diphendydrAMINE syrup with lidocaine 2% viscous. Stir well.
3. Add the Almagel Plus suspension (or equivalent). Mix thoroughly.
4. Transfer to an appropriately sized amber container.
5. Shake well.

Stable for 21 days at room temperature).

Other Medications for Mucositis: (note: this is not a formulary item and would need special authorization). Consult Pediatric Oncologist.

- Benzydamine (Tantum oral rinse) 15 ml held for at least 30 seconds then expelled QID prn (contains 10% ethanol so may sting or burn – may be avoided by diluting with equal parts of lukewarm water prior to use).
    - This product is not indicated in children under 5 years
    - This product may be considered for children undergoing head and neck radiation
    - This product has local anesthetic and anti-inflammatory properties but no antimicrobial activity

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An anonymous external review of this adapted guideline was conducted throughout Atlantic Canada by APPHON/ROHPPA. Twelve health care professionals responded to the external review, including hematologists/oncologists, nurse manager ED, registered nurses, pediatricians, pharmacists and other health care professionals. One review came from a group of multi-disciplinary health care workers.

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