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)
  - POGO Guidelines for OM Prevention in Children (2017)
- Discuss approaches to assess and manage mucositis pain in children
- Briefly review recent RCT and Clinical Trials on OM in children

Patient: "Doctor, I get a terrible pain in my eye when I drink a cup of coffee."

Doctor: "Try taking the spoon out."

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

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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

Lalla, Rajesh V., et al. "MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy." *Cancer* 120.10 (2014): 1453-1461.

- 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

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

Adapted from Somerfield MR, Padberg JR, Pfister DG, et al. ASCO clinical practice guidelines: process, progress, pitfalls, and prospects. *Class Pap Curr Comments*. 2000;4:881-886.[21]

TABLE 2. Criteria for Each Guideline Category

Recommendation	Reserved for guidelines that are based on level I or level II evidence.
Suggestion	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.
No guideline possible	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.

Evidence Strength	FOR	AGAINST
Strong	Recommends	Do NOT use
Weaker	Favors	Did NOT support
Insufficient	No Guideline possible	

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

RECOMMENDATIONS IN FAVOR OF AN INTERVENTION (ie, 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/cm^2), 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 benzydamine 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 (ie, 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% doxepin 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 (ie, strong evidence indicates lack of effectiveness in the treatment setting listed):

1. The panel *recommends* that PTA (polymyxin, tobramycin, amphotericin B) and BCoG (bacitracin, clotrimazole, gentamicin) 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 kegaran antimicrobial mouthwash *not* 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 (I), or in patients receiving radiation therapy (I) 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 (I), 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 (ie, 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 (II).
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 pentoxifylline, 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, grays; HSCT, hematopoietic stem cell transplantation; MASCC/ISOO, Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology; mW, milliwatt; nm, nanometers.

[a]Level of evidence for each guideline is in brackets after the guideline statement.

MASCC/ISOO Clinical Practice Guidelines for OM 2014

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

MASCC/ISOO Clinical Practice Guidelines for OM 2014

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

Evidence Strength	FOR	AGAINST
Strong	Recommends	Do NOT use
Weaker	Favors	Did NOT support
Insufficient	No Guideline possible	

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

Biswas, Kumar, et al. "A mediated model of the effects of human resource management policies and practices on the intention to promote women: An investigation of the theory of planned behaviour." The International Journal of Human Resource Management 28.9 (2017): 1309-1331.

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

Saline
Sodium bicarbonate
Mixed medication mouthwashes
Calcium phosphate
Chlorhexidine with chemo

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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, anesthe
5. Laser and other light therapy (PBM)
6. Cryotherapy
7. Natural and miscellaneous agents

GMCSF 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

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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 analges
5. Laser and other light therapy (PBM)
6. Cryotherapy
7. Natural and miscellaneous agents

Aspirin
OrgoteinAzelastine
Mesalazine
Prostaglandin E2
Immunoglobulins
Corticosteroids
Indomethacin
Flurbiprofen
Histamine
Colchicine
Placentrex

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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

Acyclovir
Clarithromycin
Nystatin
Kefir
Povidone-iodine
Fluconazole
Topical Na Hyaluronate
Cocaine
Amethocaine
Capsaicin
Methadone
Ketamine
Nortryptiline
Gabapentin

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

1. Basic oral care
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**

Allopurinol
Payayor
RT timing
Bethanechol
Midline mucosa-sparing RT blocks
Chewing gum
Propantheline
Tetrachlorodecaoxide

- **Favors zinc** to ***prevent*** OM with chemo +/- RT for **oral cancer**
- **Do NOT use IV Glutamine** to ***prevent*** OM w/ HD chemo ± TBI for **H**
- No guideline for other **natural agents** d/t conflicting evidence
- **Do NOT use Pilocarpine** to ***prevent*** OM w/ RT +/- TBI in H&NC, or c[illegible]o ± TBI for HCT
- **Do NOT use Oral Pentoxifylline** to ***prevent*** OM w/ HCT
- No guideline for other misc. agents d/t inadequate/conflicting evidence

Children are not just little adults

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- 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

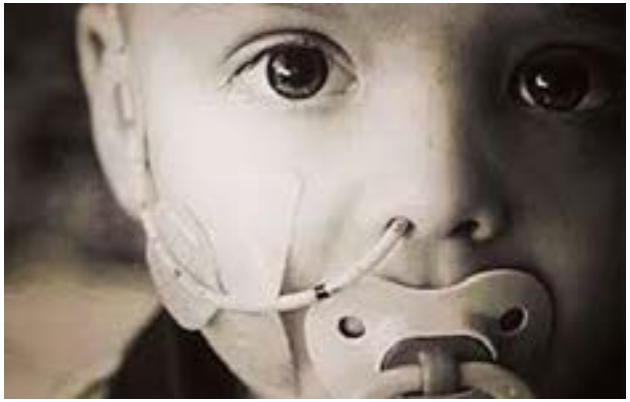
- Patient-related
- Treatment-related

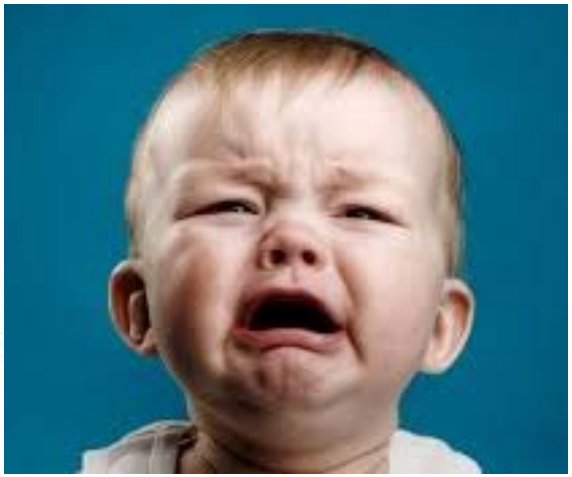
Regimen
Dose
Route
Frequency of Administration
Short vs long duration of bolus
Excretion in saliva
Methotrexate, Etoposide
Absolute Neutrophil Count
Duration of neutropenia

Chemo commonly assoc. w/ OM in children

Cytarabine
Doxorubicin
Etoposide
Melphalan
Methotrexate

Children are not just little adults





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Evidence re: Mucositis in Children Receiving Cancer Therapy or HCT

Pediatric Oncology Group of Ontario (POGO) Mucositis Prevention Guideline Development Group 2017[a]

- 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

a. Sung L, Robinson P, Treister N, et al. *BMJ Supportive & Palliative Care* 2017;7:7–16. https://onlinelibrary.wiley.com/doi/full/10.1002/cncr.20163

b. Worthington HV, Clarkson JE, Bryan G, et al. Interventions for preventing oral mucositis for patients with cancer receiving treatment. *Cochrane Database Syst Rev* 2011;(4):CD000978. https://doi.org/10.1002/14651858.CD000978.pub5

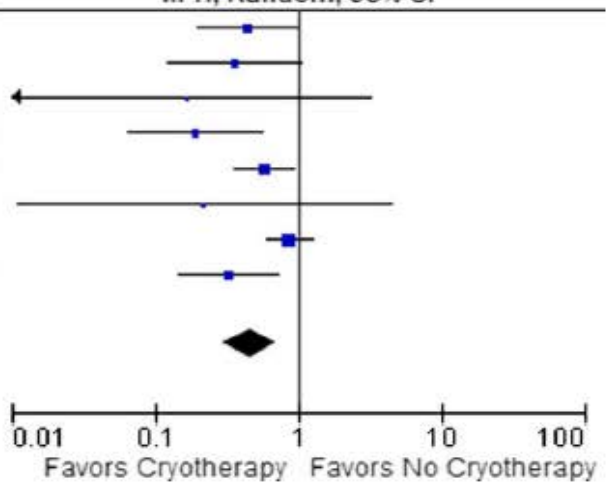
Summary of POGO Recommendations

1. **<u>Cryotherapy</u>** 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)

	Cryotherapy		No Cryotherapy			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Mahood 1991	7	50	14	45	14.4%	0.45 [0.20, 1.01]	1991
Casinu 1994	4	44	10	40	10.3%	0.36 [0.12, 1.07]	1994
Baydar 2005	0	45	3	54	2.0%	0.17 [0.01, 3.22]	2005
Lilleby 2006	3	21	14	19	10.3%	0.19 [0.07, 0.57]	2006
Svanberg 2007	14	39	24	39	21.5%	0.58 [0.36, 0.95]	2007
Papadeas 2007	0	36	2	40	1.9%	0.22 [0.01, 4.47]	2007
Gori 2007	29	62	32	60	24.7%	0.88 [0.61, 1.25]	2007
Sorensen 2008	7	67	21	66	14.9%	0.33 [0.15, 0.72]	2008
Total (95% CI)		**364**		**363**	**100.0%**	**0.46 [0.30, 0.71]**	
Total events	64		120				

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 14.49$, $df = 7$ ($P = 0.04$); $I^2 = 52\%$

Test for overall effect: $Z = 3.50$ ($P = 0.0005$)



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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

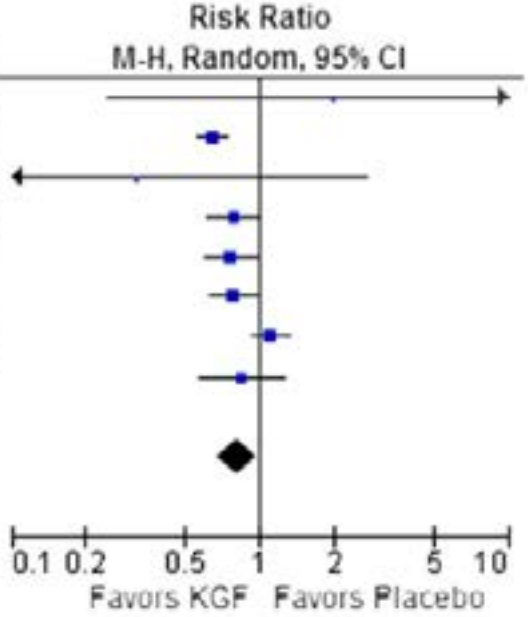
C. Oberoi S, Zamperlini-Netto G, Beyene J, et al. Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis. PLoS ONE 2014;9:e107418. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0107418

Summary of POGO Recommendations

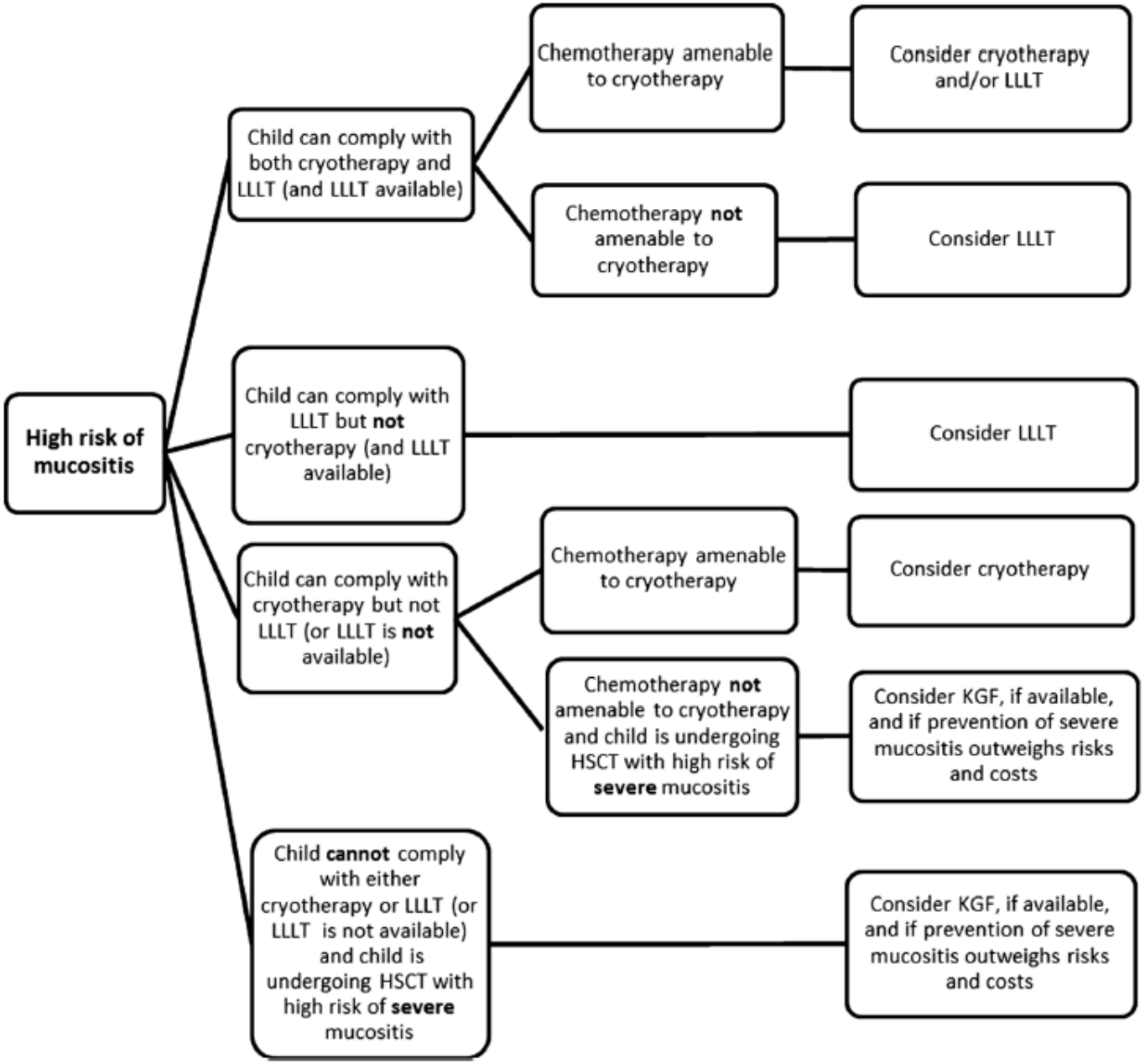
3. **KGF** may be offered to children receiving HSCT regimens assoc. with high rate of severe OM→ *weak, high-quality of evidence*
   - Lack pediatric-specific efficacy and toxicity, but high value based on adult evidence
   - Theoretical concern that young children have increase risk of adverse effects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

	KGF		Placebo			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Freytes 2004	4	28	1	14	0.7%	2.00 [0.25, 16.26]	2004
Spielberger 2004	67	106	104	106	19.7%	0.64 [0.56, 0.75]	2004
Rosen 2006	1	28	4	36	0.7%	0.32 [0.04, 2.72]	2006
Brizel 2008	43	67	26	32	16.1%	0.79 [0.62, 1.01]	2008
Henke 2011	47	92	63	94	16.1%	0.76 [0.60, 0.97]	2011
Le 2011	51	94	65	94	16.7%	0.78 [0.62, 0.99]	2011
Jagasia 2012	62	77	57	78	18.8%	1.10 [0.93, 1.31]	2012
Blijlevens 2013	70	224	21	57	11.1%	0.85 [0.57, 1.25]	2013
Total (95% CI)		**716**		**511**	**100.0%**	**0.81 [0.67, 0.97]**	
Total events	345		341				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 23.00$, $df = 7$ ($P = 0.002$); $I^2 = 70\%$
Test for overall effect: $Z = 2.27$ ($P = 0.02$)



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

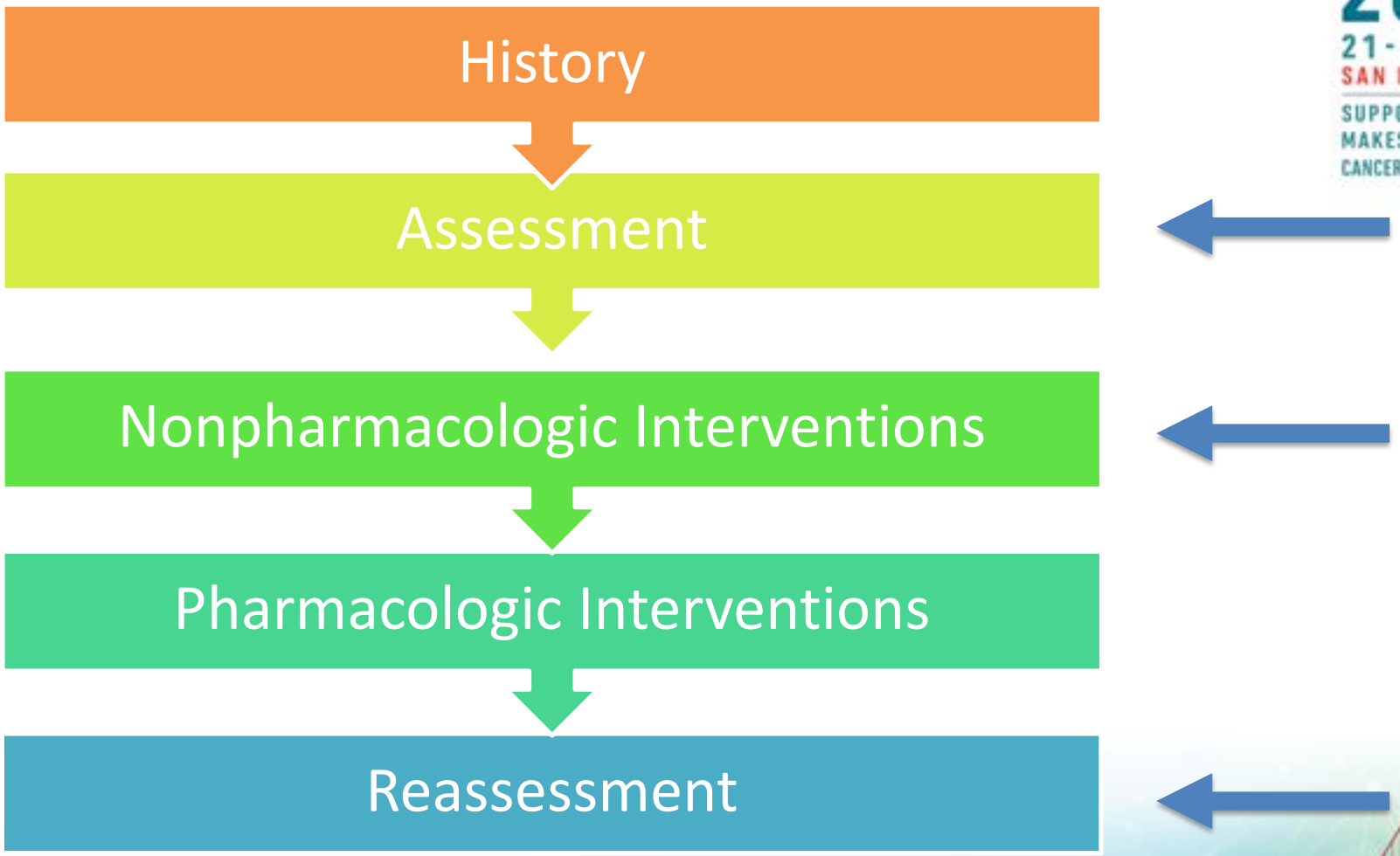
Fundamental Principles of Pediatric Pain Management

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



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Variables Used to Assess Pain in Children

- Physiologic

· Heart rate	· Oxygen saturation
· Blood pressure	· Tonicity
· Respiratory rate	

- Behavioral

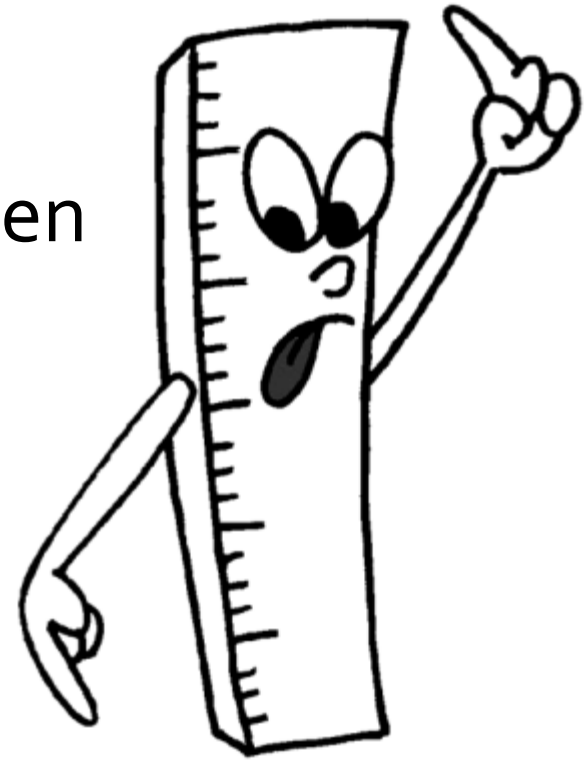
· Consolability	· Regressive behaviors
· Activity level	· Disinterest in play
· Posture/position	· Disinterest in self

- Subjective

· Child
· Parent
· Clinicians

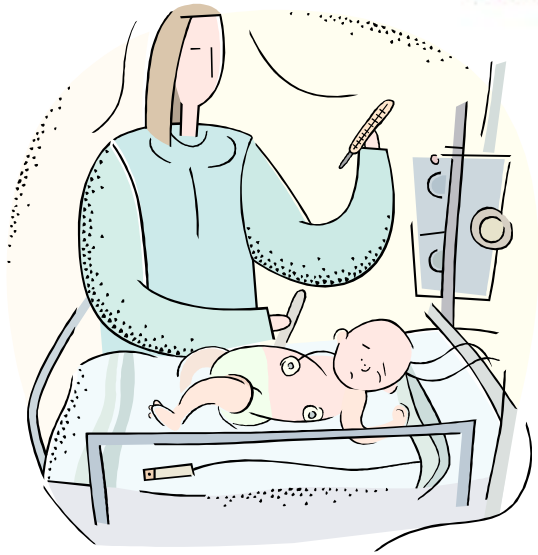
Instruments to Assess Pain in Children

- 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)

Parameter	Finding	Points
Facial Expression	Relaxed	0
	Grimaced	1
Cry	No cry	0
	Whimper	1
	Vigorous cry	2
Breathing	Relaxed	0
	Altered	1
Arms	Relaxed	0
	Flexed/extended	1
Legs	Relaxed	0
	Flexed/extended	1
State of arousal	Sleeping/awake	0
	Fussy	1



Faces Scale: > 6 years

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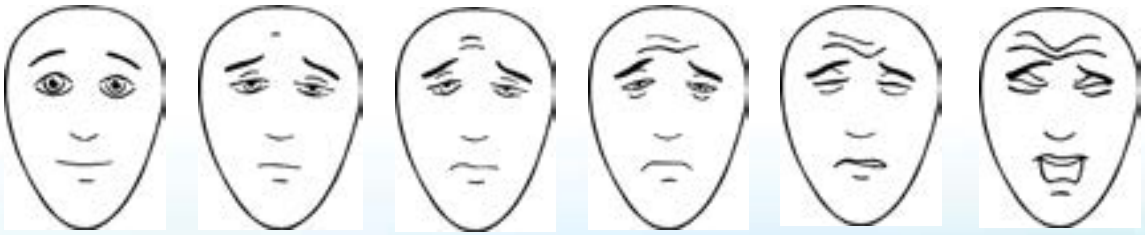
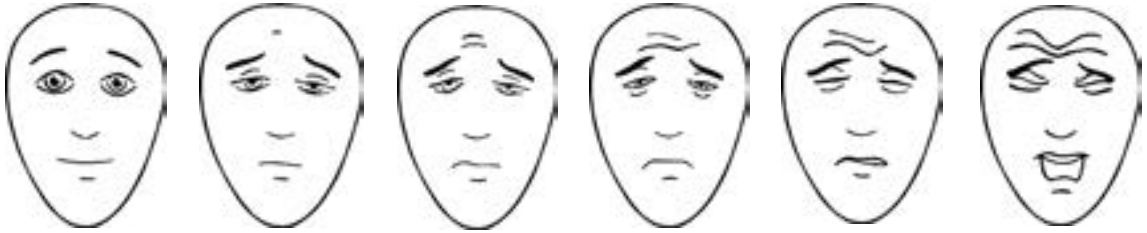
Wong-Baker Faces

Faces Pain Scale – Revised 2001



Faces Pain Scale - Revised



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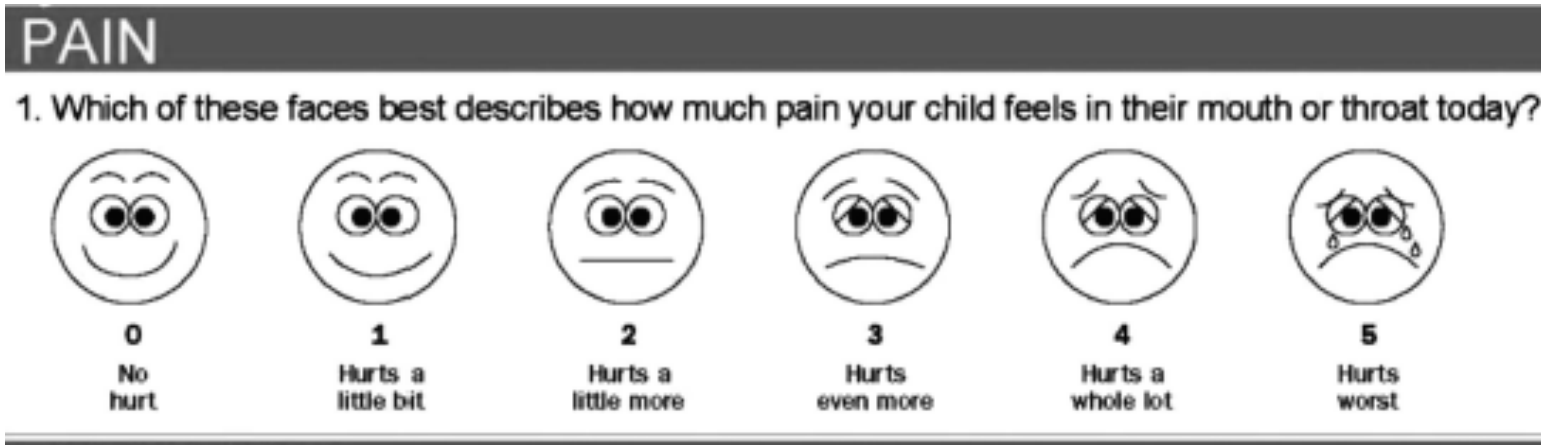
This scale is intended to measure how children feel INSIDE, not how their face looks

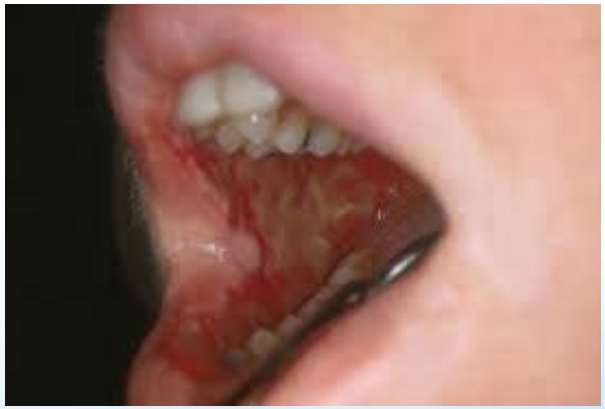
"These faces show how much something can hurt. This face (point to left-most face) shows no pain. The faces show more and more pain (point to each from left to right) up to this one (point to right most). It shows very much pain. Point to the face that shows how much you hurt (right now)."

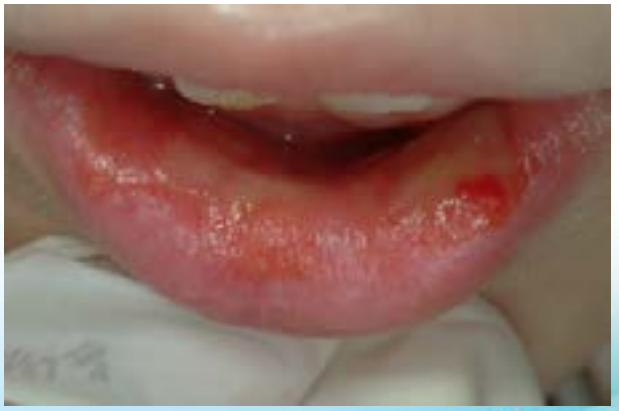
Assessing mucositis pain in children

Children's International Mucositis Evaluation Scale (ChIMES)

S Jacobs, C Baggott, R Agarwal, L Sung, et al. *British Journal of Cancer* (2013) 109: 515–2522





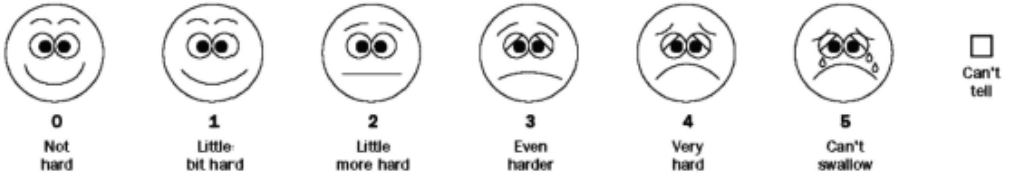


PAIN

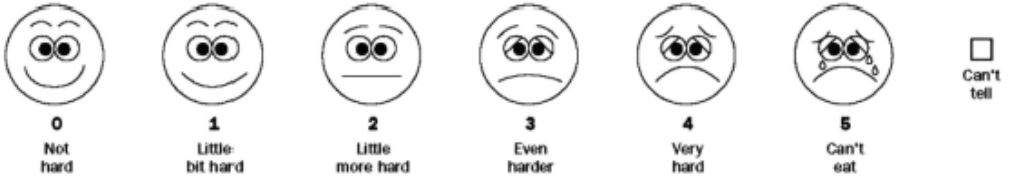
1. Which of these faces best describes how much pain your child feels in their mouth or throat today? Circle one.

FUNCTION

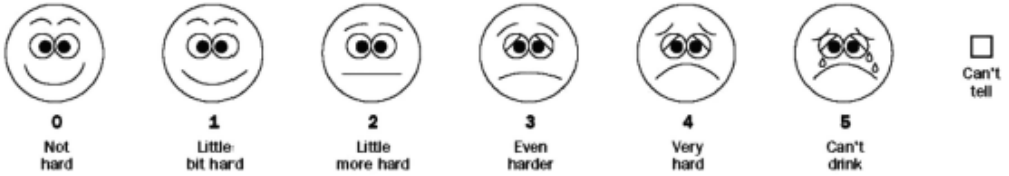
2. Which of these faces shows how hard it is for your child to SWALLOW their saliva/spit today because of mouth or throat pain? Circle one.



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



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



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

Pain

Swallow

Eat

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

Drink

Use of pain med

Visual assessment

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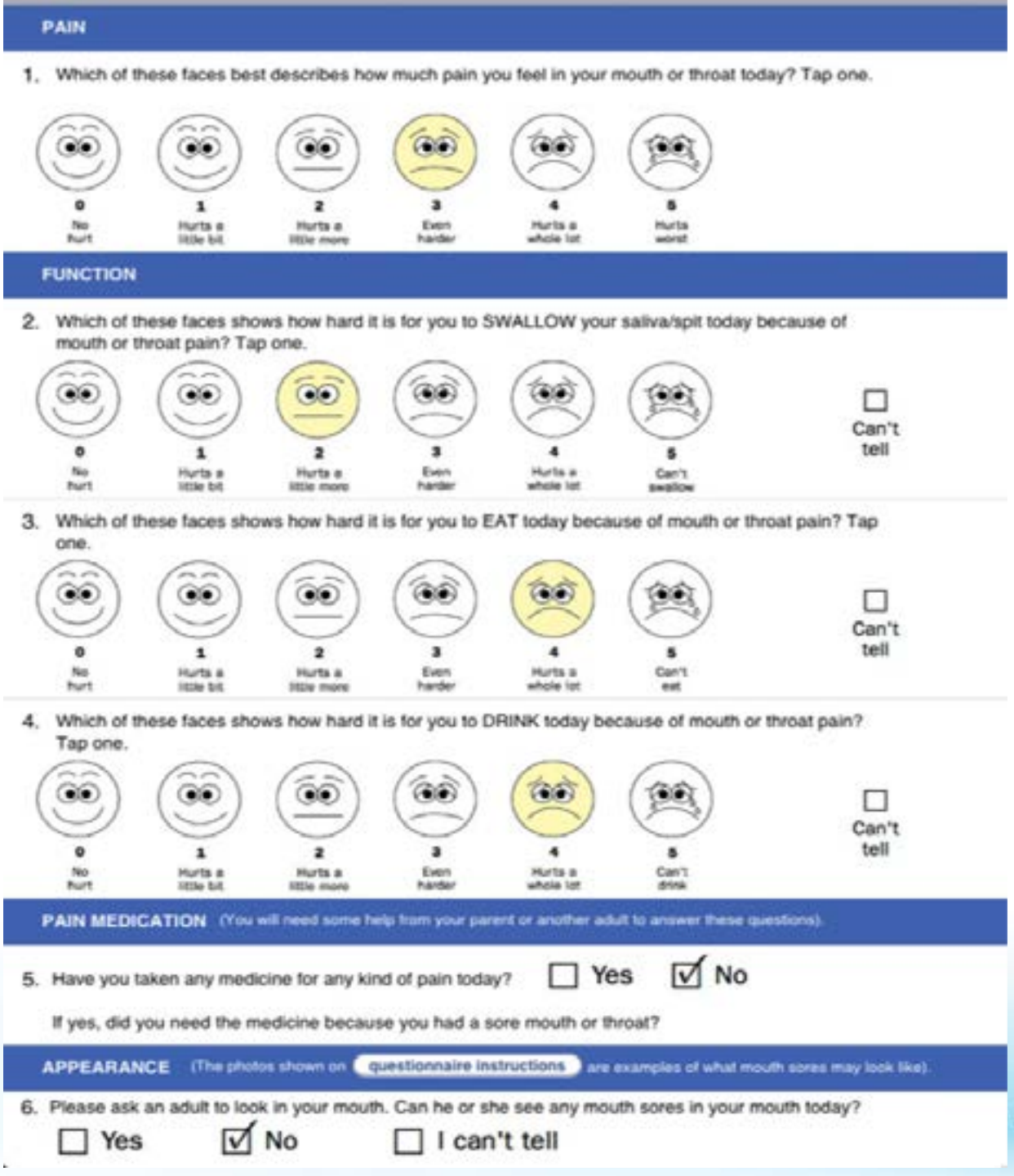

PAIN

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 Even harder · 4 Hurts a whole lot · 5 Hurts worst

FUNCTION

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 Even harder · 4 Hurts a whole lot · 5 Can't swallow · ☐ Can't tell

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 Even harder · 4 Hurts a whole lot · 5 Can't eat · ☐ Can't tell

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 Even harder · 4 Hurts a whole lot · 5 Can't drink · ☐ Can't tell

PAIN MEDICATION (You will need some help from your parent or another adult to answer these questions).

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

If yes, did you need the medicine because you had a sore mouth or throat?

APPEARANCE (The photos shown on questionnaire instructions are examples of what mouth sores may look like).

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

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eChIMES

Tomlinson, D., Hesser, T., Maloney, AM. et al. Support Care Cancer (2014) 22: 115. https://doi.org/10.1007/s00520-013-1953-x

Common Non-Pharmacologic Strategies

Comfort Measures - pacifier, swaddling, sucrose pacifiers	Guided Imagery - music, emotive imagery, special place
Distraction - reading, bubbles, video games, music	Progressive Muscle Relaxation
Breathing Techniques - patterned, shallow, rhythmic	Self-hypnosis/self-regulation activities

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

Pediatric Clinics of North America, 2007; 54(5): 645-672.

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

Pediatric Clinics of North America, 2007; 54(5): 645-672.

Pharmacologic Treatment of Pain in Children

- Local Anesthetics and Topical Analgesics
- Acetaminophen and NSAIDS
- Opioids
- Combination Medications

Topical Agents for Mucositis Pain in Children

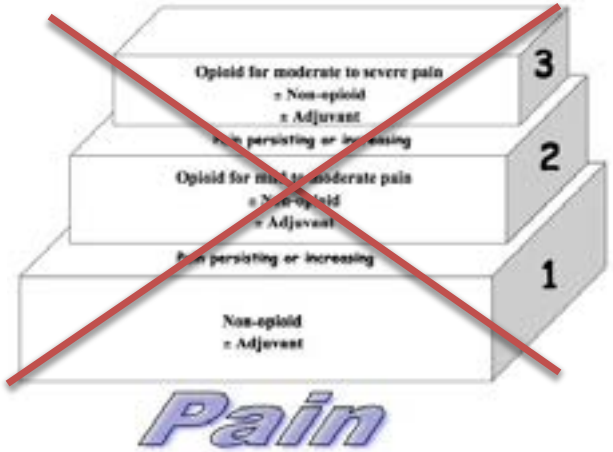
- Bland rinses
  - Saline
  - Hydrogen peroxide
- Viscous lidocaine
- Single dose of lidocaine 2% (5 ml swish and spit)
- Benzydamine topical rinse
- Lip balms, salves, and other coating agents

- No significant evidence to support use of mouthwashes often called "magic mouthwash"

2012 WHO Ladder to Treat Pain in Children

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

Persisting pain in children package: WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses.

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

Constipation	Itching
Nausea/Vomiting	Confusion
Myoclonus	Somnolence
Respiratory depression	

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

Patient Age	Max Dose of IV Morphine
Infant	2 mg/dose
Children 1-6 yo	4 mg/dose
Children 7-12 yo	8 mg/dose
Adolescent	10 mg/dose

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

Received: 5 December 2018 | Revised: 21 February 2019 | Accepted: 24 February 2019

DOI: 10.1002/pbc.27698

Pediatric Blood & Cancer | aspho | WILEY

CLINICAL PRACTICE GUIDELINES

Reducing pain in children with cancer: Methodology for the development of a clinical practice guideline

Erik A.H. Loeffen[1] | Leontien C.M. Kremer[2,3] | Marianne D. van de Wetering[2] | Renée L. Mulder[2,3] | Anna Font-Gonzalez[2,3] | Lee L. Dupuis[4,5] | Fiona Campbell[6] | Wim J.E. Tissing[1,2] | on behalf of the Pain in Children with Cancer Guideline Development Panel*

https://doi.org/10.1002/pbc.27698 First published March 2019

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"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."

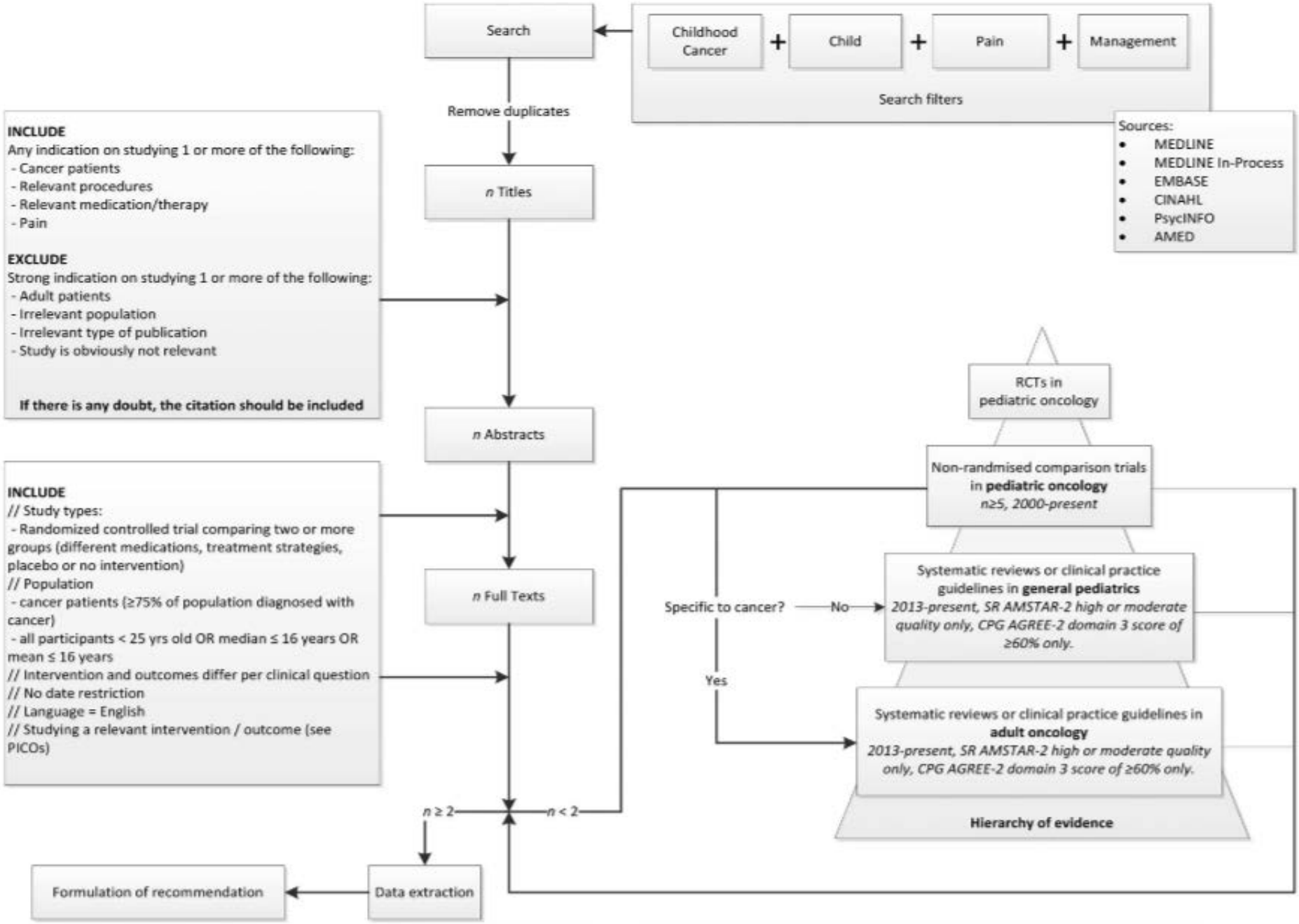

FIGURE 2 Flowchart of the study search and selection regarding clinical questions on the management of pain in children with cancer

CLINICAL PRACTICE GUIDELINES

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Reducing pain in children with cancer: Methodology for the development of a clinical practice guideline

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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

37. Bardellini E, Amadori F, Schumacher RF, D'Ippolito C, Porta F, Majorana A. Efficacy of a solution composed by verbascoside, polyvinylpyrrolidone (PVP) and sodium hyaluronate in the treatment of chemotherapy-induced oral mucositis in children with acute lymphoblastic leukemia. *J Pediatr Hematol Oncol*. 2016;38(7):559-562.

38. Cheng KKF, Chang AM. Palliation of oral mucositis symptoms in pediatric patients treated with cancer chemotherapy. *Cancer Nurs*. 2003;26(6):476-484.

39. Collins JJ, Grier HE, Sethna NF, Wilder RT, Berde CB. Regional anesthesia for pain associated with terminal pediatric malignancy. *Pain*. 1996;65(1):63-69.

40. Oudot C, Laplanche A, Orbach D, et al. PCA analgesia for children with chemotherapy-related mucositis: a double-blind randomized comparison of morphine and pethidine. *Bull Cancer*. 2011;98(2):E11-E18.

41. Raphael MF, Den Boer AM, Abbink FCH, et al. Caphosol, a therapeutic option in case of cancer therapy-induced oral mucositis in children? Results from a prospective multicenter double blind randomized controlled trial. *Support Care Cancer*. 2013;21:S158-S159.

2019 21-23 JUNE SAN FRANCISCO SUPPORTIVE CARE MAKES EXCELLENT CANCER CARE POSSIBLE

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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)

He, Mengxue, et al. "A systematic review and meta-analysis of the effect of low-level laser therapy (LLLT) on chemotherapy-induced oral mucositis in pediatric and young patients." *European journal of pediatrics* 177.1 (2018): 7-17.

- 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

1. Gobbo, Margherita, et al. "Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT." *Pediatric blood & cancer* 65.8 (2018): e27098.
2. João Batista Medeiros-Filho, et al. Laser and photochemotherapy for the treatment of oral mucositis in young patients: Randomized clinical trial: *Photodiagnosis and Photodynamic Therapy*, Volume 18, 2017, pp. 39-45
3. Vânia Cavalcanti Ribeiro da Silva et al. Photodynamic therapy for treatment of oral mucositis: Pilot study with pediatric patients undergoing chemotherapy: *Photodiagnosis and Photodynamic Therapy*, Volume 21, 2018, pp. 115-120
4. Boris SP et al. Photobiomodulation of tissues of the oral cavity for prevention and treatment of mucositis associated with polychemotherapy in children. *Pediatric Hematology/Oncology and Immunopathology*. 2016;15(3):29-33. (In Russ.)
5. Vitale, M.C.,et al. Preliminary study in a new protocol for the treatment of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) and chemotherapy (CT) *Lasers Med Sci* (2017) 32: 1423.
6. Ribeiro, I.L.A.; Limeira, R.R.T.; Dias de Castro, R.; Ferreti Bonan, P.R.; Valença, A.M.G. Oral Mucositis in Pediatric Patients in Treatment for Acute Lymphoblastic Leukemia. *Int. J. Environ. Res. Public Health* **2017**, *14*, 1468.

Photobiomodulation Update: Prevention

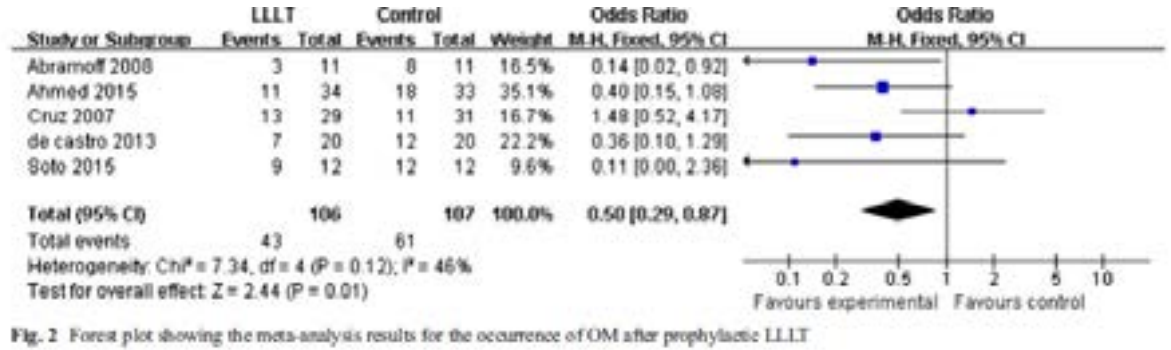


Fig. 2 Forest plot showing the meta-analysis results for the occurrence of OM after prophylactic LLLT

OM Occurrence

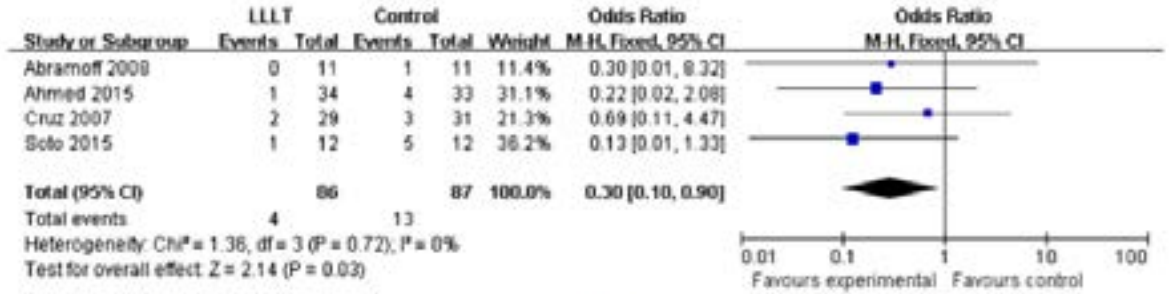


Fig. 3 Forest plot showing the meta-analysis results for the occurrence of grade III or higher OM after prophylactic LLLT

Occurrence of greater than Grade III OM

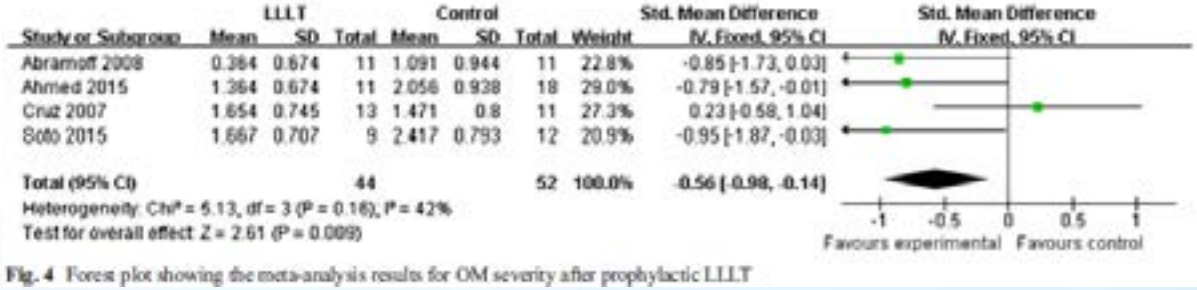


Fig. 4 Forest plot showing the meta-analysis results for OM severity after prophylactic LLLT

Occurrence of severe OM

He, Mengxue, et al. "A systematic review and meta-analysis of the effect of low-level laser therapy (LLLT) on chemotherapy-induced oral mucositis in pediatric and young patients." *European journal of pediatrics* 177.1 (2018): 7-17.

Photobiomodulation Update: Treatment

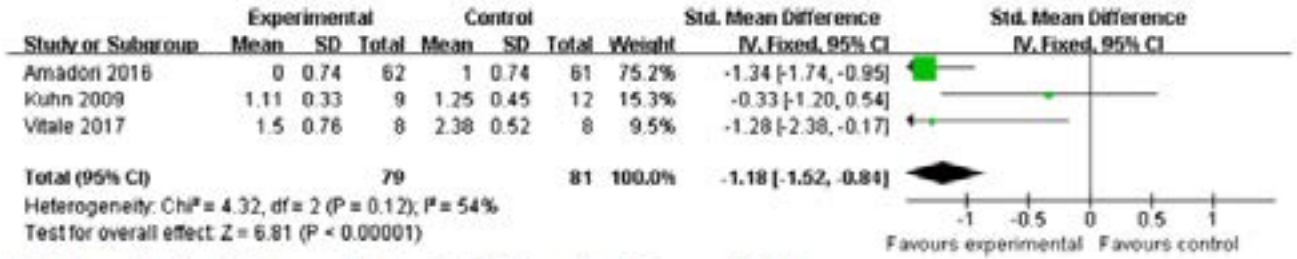


Fig. 5 Forest plot showing the meta-analysis results for OM severity after therapeutic LLLT

OM severity

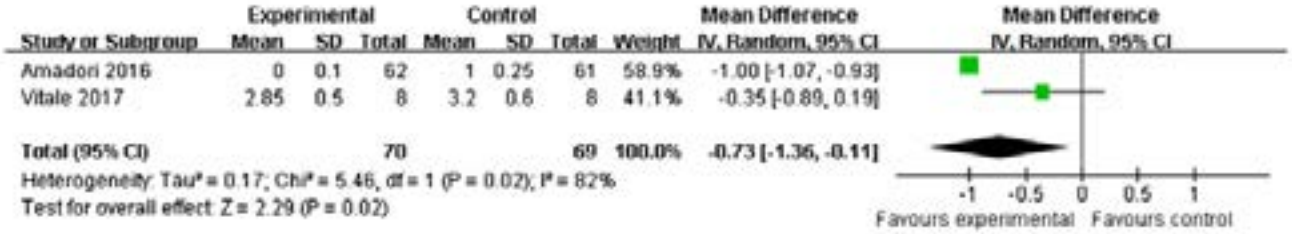


Fig. 6 Forest plot showing the meta-analysis results for oral pain after therapeutic LLLT

Degree of OM-related oral pain

He, Mengxue, et al. "A systematic review and meta-analysis of the effect of low-level laser therapy (LLLT) on chemotherapy-induced oral mucositis in pediatric and young patients." *European journal of pediatrics* 177.1 (2018): 7-17.

Photobiomodulation Update

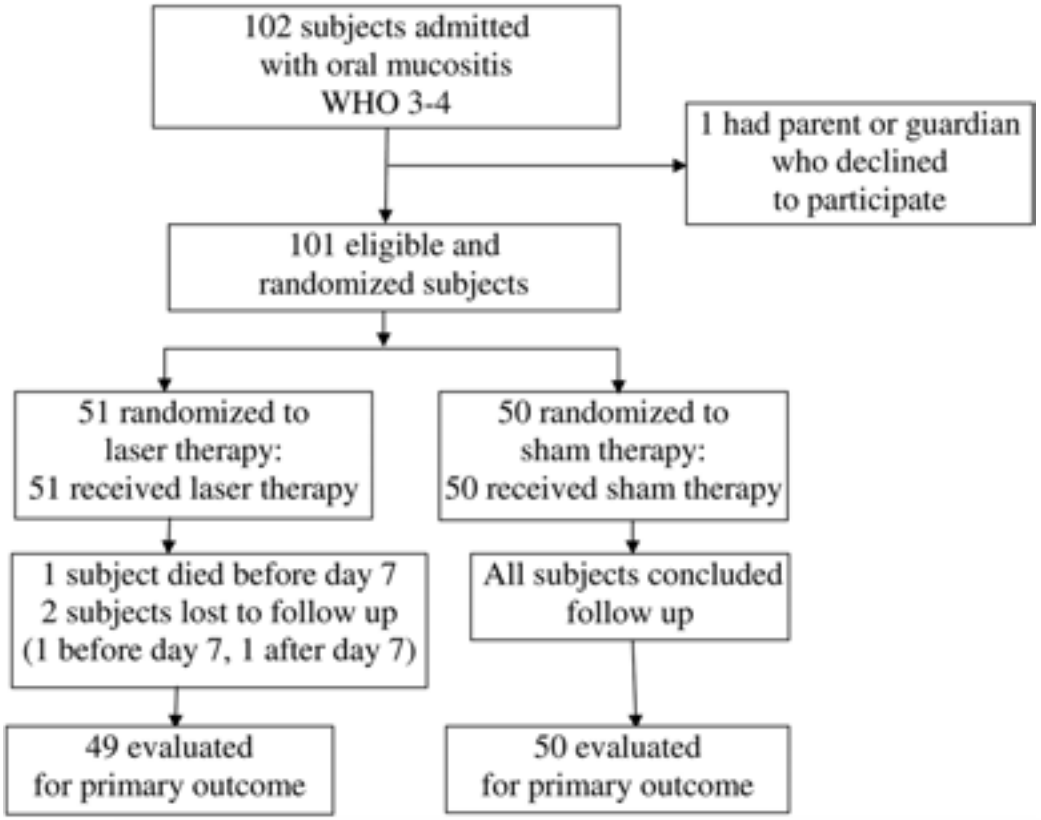
The basic disease and methods of treatment	Age of patients, years	Laser therapy methods	Development of complications, %		Source
			After LLLT	Without LLLT	
A randomized, prospective, controlled trial during 93 sessions of chemotherapy with highdose methotrexate for acute lymphoblastic leukemia or lymphoma involved 33 children: 17 - main group, 16 - comparison group	The main, 1.7-17.9 (Av. age - 5.9) Comparison group 1.2-16.3 (Av. age - 8.4)	λ = 670 nm, HP, M = 30 mW, S = 0.5cm^2; E = 12-24 secs per one zone. For prevention, each of the 13 affected areas were consistently illuminated: the left and right cheek tissues along the line of teeth closing, the retromolar space, the lateral and ventral surfaces of the tongue, and the palate, upper and lower lips.	59	88	Boris S.P. et al., 2016 [16]

Moskvin, Sergey, et al. "A brief literature review and own clinical experience in prophylaxis of oral mucositis in children using low level laser therapy." *BioMedicine* 9.1 (2019).

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

[16] Photobiomodulation of tissues of the oral cavity for prevention and treatment of mucositis associated with polychemotherapy in children. *Pediatric Hematology/Oncology and Immunopathology*. 2016;15(3):29-33. (In Russ.)

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

Gobbo M, Verzegnassi F, Ronfani L, et al. Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT. *Pediatr Blood Cancer*. 2018;65:e27098. https://doi.org/10.1002/pbc.27098

PBM to ***TREAT*** Mucositis Pain in Children

TABLE 2 Study results

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

Gobbo M, Verzegnassi F, Ronfani L, et al. Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT. *Pediatr Blood Cancer*. 2018;65:e27098. https://doi.org/10.1002/pbc.27098

PBM to ***TREAT*** Mucositis Pain in Children

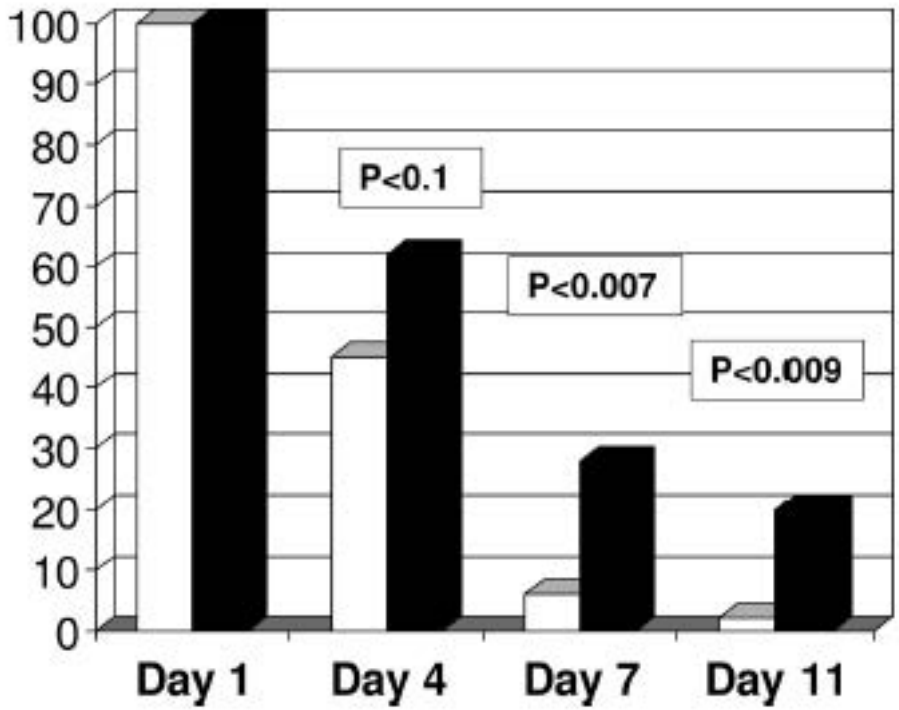


FIGURE 2 Percentage of patients with OM grade 3–4 in the PBM group (white columns) and sham group (black columns) on days +1, +4, +7, and +11

Gobbo M, Verzegnassi F, Ronfani L, et al. Multicenter randomized, double-blind controlled trial to evaluate the efficacy of laser therapy for the treatment of severe oral mucositis induced by chemotherapy in children: laMPO RCT. *Pediatr Blood Cancer*. 2018;65:e27098. https://doi.org/10.1002/pbc.27098

Photobiomodulation Update: Treatment
High-Power Laser Therapy (Pilot Clinical Trial)

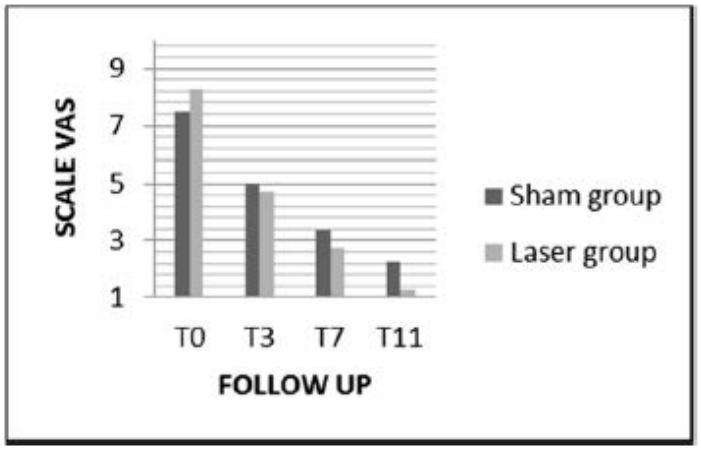


Fig. 1 Visual analogue scale—VAS score progression between day 0 and day 11

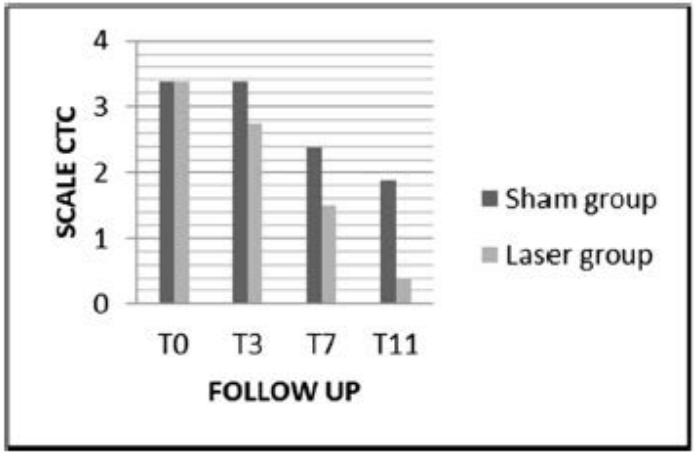
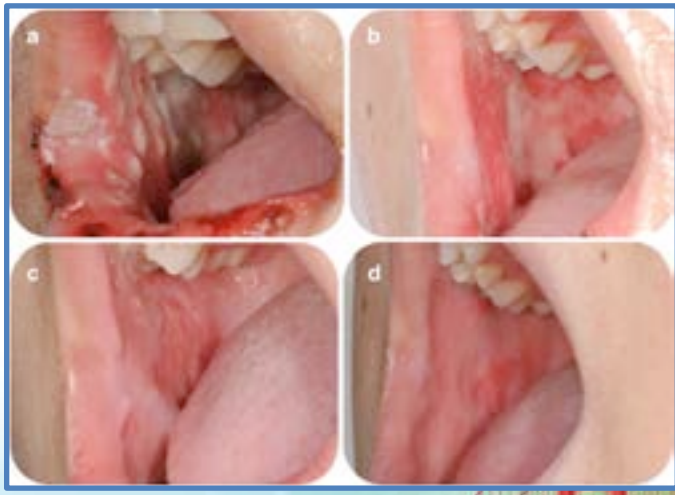


Fig. 2 Mucositis scale—CTC score progression between day 0 and day 11

- 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)



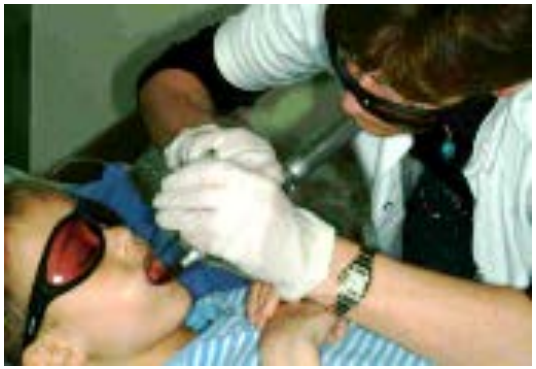
Vitale, Marina Consuelo, et al. "Preliminary study in a new protocol for the treatment of oral mucositis in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) and chemotherapy (CT)." *Lasers in medical science* 32.6 (2017): 1423-1428.

Photobiomodulation Update

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

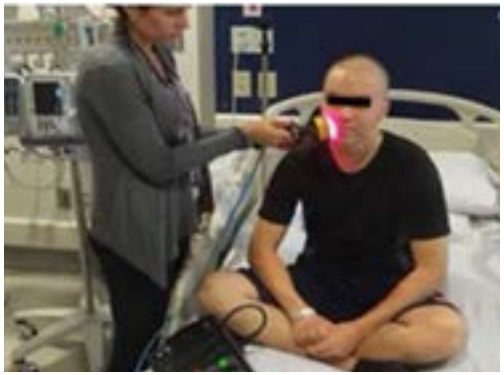
1. Anna N. Yaroslavsky, Nathaniel S. Treister et al, "A Monte Carlo simulation of the dosimetry of extraorally delivered photobiomodulation therapy (Conference Presentation)," Proc. SPIE 10477, Mechanisms of Photobiomodulation Therapy XIII, 104770H (14 March 2018);

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?

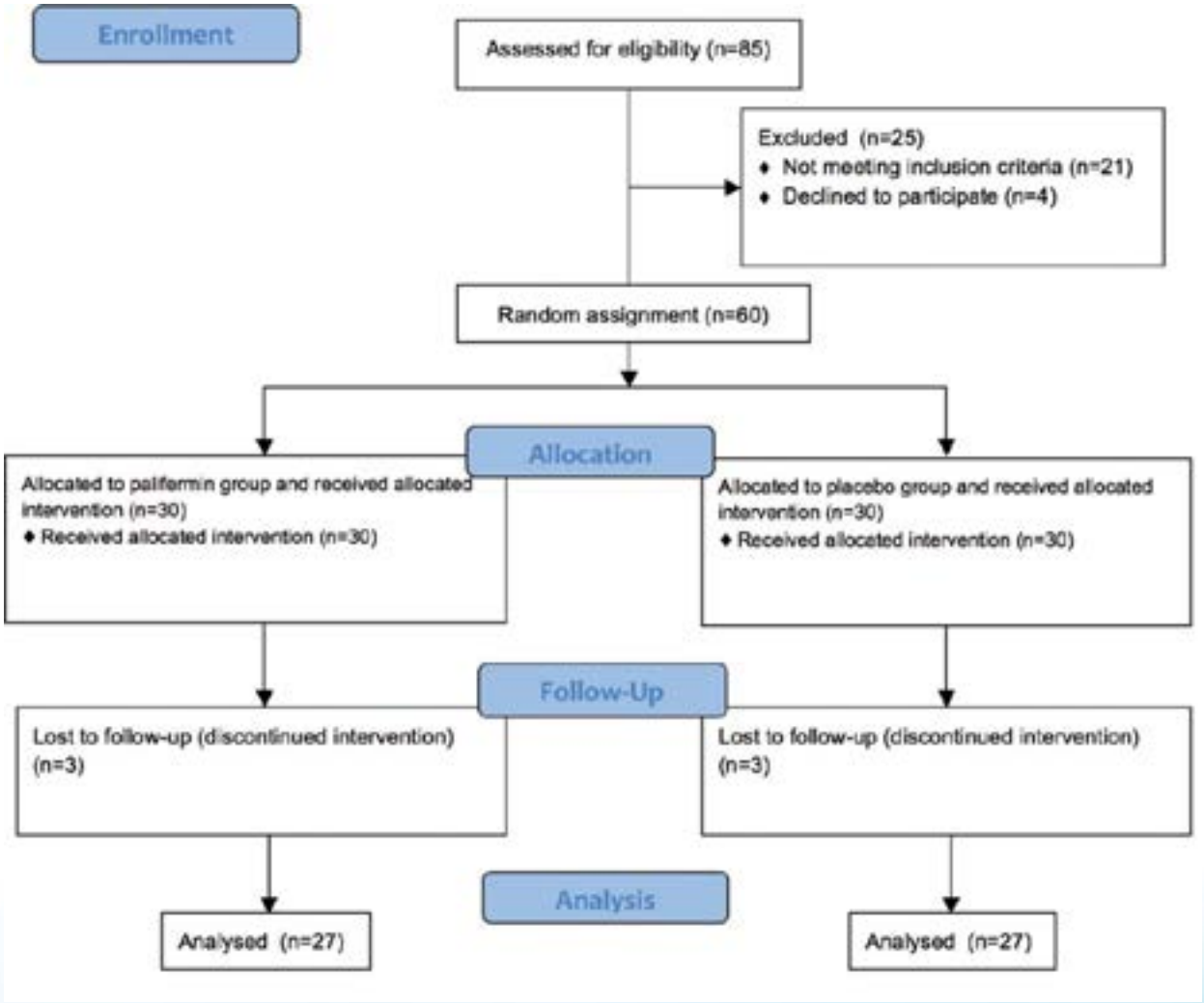


Extraoral

- 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

Alessandra Lucchese et al Efficacy and effects of palifermin for the treatment of oral mucositis in patients affected by acute lymphoblastic leukemia, *Leukemia & Lymphoma*, 57:4, 820-827, (2016) DOI: 10.3109/10428194.2015.1081192

Use of KGF for Children Receiving HCT

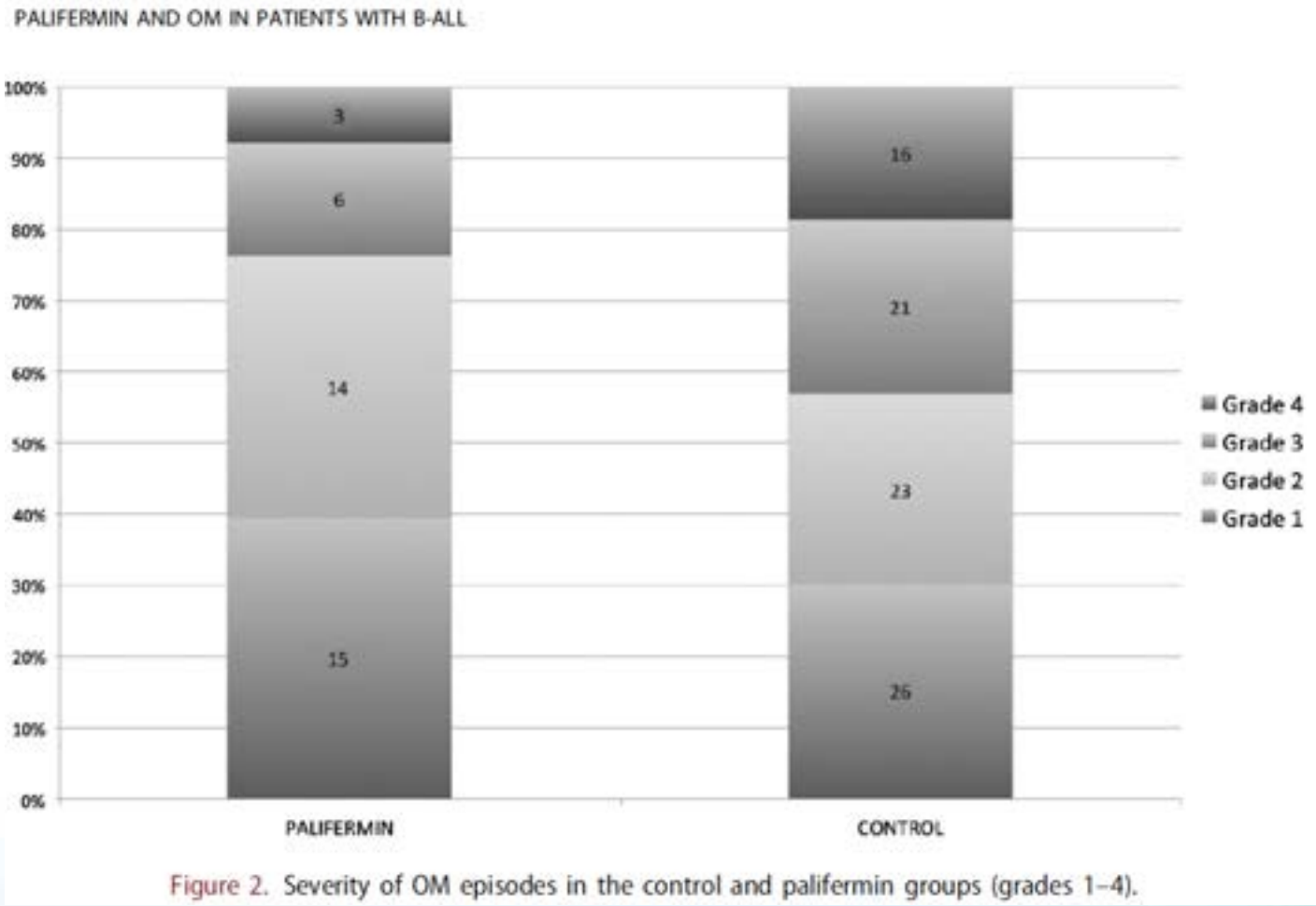


Figure 2. Severity of OM episodes in the control and palifermin groups (grades 1–4).

Alessandra Lucchese et al Efficacy and effects of palifermin for the treatment of oral mucositis in patients affected by acute lymphoblastic leukemia, *Leukemia & Lymphoma*, 57:4, 820-827, (2016) DOI: 10.3109/10428194.2015.1081192

Use of KGF for Children Receiving HCT

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

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

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.

	Scale	Palifermin group ($n = 27$)	Control group ($n = 27$)	p value
Sleeping, mean (SD)	0–5	1 (0.6)	3 (1.1)	≤0.001
Swallowing, mean (SD)	0–5	1 (0.5)	4 (0.8)	≤0.001
Drinking, mean (SD)	0–5	1 (0.3)	4 (1.1)	≤0.001
Eating, mean (SD)	0–5	2 (0.4)	3 (33)	≤0.001
Talking, mean (SD)	0–5	0 (0.2)	3 (0.2)	≤0.001

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

Alessandra Lucchese et al Efficacy and effects of palifermin for the treatment of oral mucositis in patients affected by acute lymphoblastic leukemia, *Leukemia & Lymphoma*, 57:4, 820-827, (2016) DOI: 10.3109/10428194.2015.1081192

2019
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SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

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

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