Preliminary Guidelines Presentation

- Anti-inflammatory
- Basic Oral Care
- Laser and Light Therapy

Section: Anti-inflammatory

- Benzydamine
- Celecoxib
- Irsogladine maleate
- Misoprostol
- Rebmipide

Benzydamine (rinse): H&N – RT (<50 Gy) - Prevention
Guideline: Recommendation

Route of Administration	Cancer Type	Treatment Modality	Indication	Author, Year	Effective	Overall Level of Evidence	Non-RCT studies
Mouth wash	H&N	RT	P	Epstein 1986 [24]	Y	I	
				Epstein 1989[22]	Y		
				Epstein 2001[26]	Y		
				Kazemian 2009[25]	Y		
				Jayachandran 2012 [23]	N		

Benzydamine (rinse): H&N – RT-CT - Prevention Guideline: Recommendation

Route of Administration	Cancer Type	Treatment Modality	Indication	Author, Year	Effective (Yes/No)	Overall Level of Evidence	Non-RCT studies
Mouth wash	H&N	RT-CT	P	Prada 1985[35]	Y	II	
				Prada 1987[34]	Y		
				Sheibani 2015[33]	Y		

[ES1]The previous guideline limited it up to 50 Gy. I think it was based on the Epstein 2001 study. I found on page 880-8
If so, will you agree to change the guideline wording?

Benzydamine

- (mouthwash) – H&N - RT – treatment
- (mouthwash) – hematol. & solid ca. - CT – treatment

- Guideline: No guideline possible

Misoprostol

- Misoprostol (PO) – hematol. & solid ca. - CT – prevention
- Misoprostol (topical) – hematol. & solid ca. - CT – prevention
- Misoprostol (topical) – H&N - RT – prevention
- Misoprostol (swish and swollow) – H&N - RT – prevention

- Guideline: No guideline possible

Celecoxib

- Celecoxib (PO) – H&N - RT – prevention
- Guideline: No guideline possible

Irsogladine maleate

- Irsogladine maleate (PO) – H&N - CT – prevention
- Guideline: No guideline possible

Rebmipide

- Rebmipide (gargle) – H&N – RT-CT – prevention
- Guideline: No guideline possible

Section: Basic Oral Care

- Oral care multi-agent combination protocols
- Professional care
- Patient education
- Normal saline
- Sodium bicarbonate
- Chlorhexidine, CHX (vs. placebo; vs. an active agent)

Categories

- Oral care multi-agent combination protocols
- Professional care
- Patient education
- Normal saline
- Sodium bicarbonate
- Chlorhexidine, CHX (vs. placebo; vs. an active agent)

The implementation of a regimen served to increase the awareness of both patients and staff, which would lead to better oral hygiene and indirectly less oral complications.

Categories

- Oral care multi-agent combination protocols
- Professional care
- Patient education
- Normal saline
- Sodium bicarbonate
- Chlorhexidine, CHX (vs. placebo; vs. an active agent)

Oral care delivered by dental professionals before or during cancer treatment.

Categories

- Oral care multi-agent combination protocols
- Professional care
- Patient education
- Normal saline
- Sodium bicarbonate
- Chlorhexidine, CHX (vs. placebo; vs. an active agent)

Studies that evaluated the impact of conducting customized face-face patient education on the importance of oral care during OM.

Categories

- Oral care multi-agent combination protocols
- Professional care
- Patient education
- Normal saline
- Sodium bicarbonate
- Chlorhexidine, CHX (vs. placebo; vs. an active agent)

Studies that compared saline to bland rinses or CHX to prevent and/or treat OM.

Categories

- Oral care multi-agent combination protocols
- Professional care
- Patient education
- Normal saline
- Sodium bicarbonate
- Chlorhexidine, CHX (vs. placebo; vs. an active agent)

Studies that compared sodium bicarbonate diluted in water to another bland rinses or CHX to prevent and/or treat OM.

Categories

- Oral care multi-agent combination protocols
- Professional care
- Patient education
- Normal saline
- Sodium bicarbonate
- Chlorhexidine, CHX (vs. placebo; vs. an active agent)

Studies that compared CHX to another intervention to prevent and/or treat OM.

Oral care multi-agent combination protocols

Treatment Modality	Population	Indication	RCTs Author, Year	Effective	Overall Level of Evidence	Non-RCT studies
CT	Hematol.	P	DeMorales 2001^	N	III	Levy-Polack 1998 – 3(Y) Cheng 2001 – 3(Y), Cheng & Chang 2002 – 3(Y), Chen 2004 – 5(Y)
CT +/- TBI/TLI	Hematol.	P	Kenny 1990	N	III	
RT	H&N	P	Shieh 1997	Y	III	Janjan 1992 – 3(Y)
			Kartin 2014	Y		
HSCT	Hematol. & Solid ca.	P	Borowski 1994	Y- OM severity N-OM onset & duration	III	Bhatt 2010 – 3(Y), Soga 2010 – 3(Y), Yamagata 2012-3(Y), Legert 2014 – 3(Y)

Oral care multi-agent combination protocols

- Hematol. – CT – prevention
- Guideline: Suggestion

  The consistent findings from non-RCTs suggest that the implementation of oral care multi-agent combination protocols (supervised or non-supervised) is beneficial for the prevention of OM during CT.

- H&N – RT – prevention
- Guideline: Suggestion

  The implementation of oral care multi-agent combination protocols is beneficial for the prevention of OM during H&N RT.

Oral care multi-agent combination protocols

- Hematol. & Solid cancer – HSCT – prevention
- Guideline: Suggestion

  The implementation of oral care multi-agent combination protocols is beneficial for the prevention of OM during HSCT.

Professional care

Study	Intervention Group	Control/ Comparative Group
1	• **Pre-CT dental care** • **Supervised (and assisted if needed) oral hygiene**	• **No pre-CT dental care** • **Unsupervised oral hygiene**
	• Use of mouth rinses 3 time/day with(0.12% CHLX mixed with 3% hydrogen peroxide and nystatin 100,000IU	
2	• **Professional oral health care** - scaling and polishing - weekly assessment of oral cavity - customized oral hygiene instructions	• **Self care**
3	• Pre-cancer dental care • Tooth brushing using 0.5% povidone-iodine with irrigation and suction **by dentist for 15 minutes**, 3days/ week for 2-4 weeks, followed by patient rinsing with 0.5% povidone-iodine mouthwash	• Pre-cancer dental care
	• Regular tooth brushing after meals by patient.	

Professional care

Guideline: No guideline possible

Treatment Modality	Population	Indication	RCTs Author, Year	Effective	Overall Level of Evidence	Non-RCT studies
RT	H&N	P	Spijkervet 1989	N	III	
CT	Hematol.	P	Djuric 2006	Y- Pain duration N- OM severity	III	
	Solid ca.		Saito 2014	Y		
RT & CT	H&N	P	Yoneda 2007	Y	III	Kubota 2015 – 3(Y), Yokata 2016 - 4(N)
HSCT	Hematol.	P	-	-		Melkos 2003 – 3(N), Santos 2011 – 3(N), Kashwazaki 2012 – 3(Y), Gurgan 2013 – 4(Y)

Professional care (full text)

- No guideline was possible with regards to the use of professional oral care for the prevention of OM for patients with hematologic cancers, solid cancers or H&N cancer due to limited and inconsistent data (LoE: III).
- *An expert opinion complements this guideline. Although, there was insufficient literature to support the use of professional oral care for OM prevention, the panel is of the opinion that dental evaluation and treatment (as needed) prior to cancer therapy is desirable to reduce the patient's risk of local and systemic infections from odontogenic sources.*

Patient education

Normal saline

Sodium bicarbonate

- Guideline: No guideline possible

Patient education (full text)

- No guideline was possible with regards to the use of patient education for the prevention of OM in hematologic cancer patients during HSCT or CT due to limited and inconsistent data (LoE: III).
- *An expert opinion complements this guideline. Although, there was insufficient literature to support the use of patient education for OM prevention, the panel is of the opinion that the informing patients about the benefits of BOC strategies should still be applied as this may improve patient's compliance with adhering to the oral care multi-agent combination protocol.*

Normal saline
Sodium bicarbonate (full text)

- No guideline was possible with regards to the use of saline or sodium bicarbonate rinses in the prevention or treatment of OM in patients undergoing cancer therapy due to limited data for each intervention (LoE III).
- *An expert opinion complements this guideline. Despite the limited data available for both saline and sodium bicarbonate, the panel recognizes that these rinses are frequently used in the clinical setting. The panel is of the opinion that saline and sodium bicarbonate are inert bland rinses that increase oral clearance of debris from the oral cavity which may be helpful for maintaining oral hygiene and improving patient comfort.*

Chlorhexidine (CHX)

Guideline: Suggestion (against)

The use of chlorhexidine is not suggested for the prevention of OM during H&N RT.

Treatment Modality	Population	Indication	RCTs Author, Year	Effective	Overall Level of Evidence	Non-RCT studies
RT	H&N	P	Spijkervet 1989	N	III	
	Hematol. & solid ca.		Ferretti 1990	N		
	Not stated (Likely H&N)		Foote 1994	N		

Chlorhexidine (CHX)

Additional evidence for -

- Hematol. or solid ca. – CT – Prevention
- H&N – RT-CT – prevention
- Hematol. or solid ca. – HSCT – Prevention

- Guideline: No guideline possible

Section: Laser & Light Therapy

Phases:

1. Review of clinical outcomes and study-design
   - Same methods as in all interventional sections
2. Review of physical parameters
   - Unique to this section
   - Reported physical parameters
   - Confirmation of reported physical parameters
   - Consultation with a physicist and a laser researcher
   - Interpretation of the results based on the current understanding of light-tissue interaction
3. Concluding clinical guidelines
   - Combination of evidence about clinical efficacy and reproducible laser setting parameters.

Section: Laser & Light Therapy

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Confirmation of reported physical parameters

Example

Formula:

X + X = Y

Data reported:

X = 1

Y = 3

Calculated:

1+1 = 2

Not-valid reporting

Example

Formula:

Power density (mW/cm^2) =

Fluence (J/cm2) x 1000 / time (sec)

Data reported:

- Power density = 583 mW/cm2
- Fluence = 72 J/cm2
- Time = 54 sec

Calculated :

- 72x1000 / 54 = 1333 mW/cm2
- Not valid reporting

Section: Laser & Light Therapy

Phases

1. Review of clinical outcomes and study-design
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2. Review of physical parameters
   - Unique to this section
   - Reported physical parameters
   - Confirmation of reported physical parameters
   - Consultation with a physicist and a laser researcher
   - **Interpretation of the results based on the current understanding of light-tissue interaction**
3. Concluding clinical guidelines
   - Combination of evidence about clinical efficacy and reproducible laser setting parameters.

Interpretation of the results based on the current understanding of light-tissue interaction

Example

Data reported:

- Fluence = 70 J/cm2
- Time = 20 sec
- Power = 100 W
- Spot size -0.028 cm2

Calculated – formula 1:

Power density = 100/0.028 = 3571

Calculated – formula 2:

Power density = 70x1000/20 = 3571

Template

Formula:

Power density (mW/cm^2) =

Fluence (J/cm2) x 1000 / time (sec)

Another formula:

Power density (mW/cm2) =

Power (mW) / spot size (cm2)

Valid physical setting.
However, not considered low level laser

Interpretation of the results based on the current understanding of light-tissue interaction

- Irradiance (mW/cm2) – reflects energy per spot
- Activation of biologic response, per spot.

How much of the tissue surface needs to be triggered in order to have a clinical response?

- Concept:
  - Threshold irradiance vs cumulative irradiance.
  - May be presented as cumulative fluence (J/cm2), too.

- To simplify the presentation….

  These are the physical parameters that were required:

Briefly,

Wave-length (nm)	Power (mW)	Fluence (J/cm2)	Time (sec.)	Irradiance (mW/cm2)	Spots	Cumulative fluence (J/cm2)	Effective
650	40	2	2	1000	6	12	**Y**
632.8	60	1.5	10	150	75	112.5	**Y**

Evidence clustered by cancer therapy modality

Major flaws, power analysis + physical reproducibility

No major flaws + powered + physical setting is valid = Guideline

HSCT - Prevention

Cancer treatment modality	Aim	Author, Year	Cancer type	PBM source	Wave-length (nm)	Power (mW)	Fluence (J/cm2)	Time (sec.)	Irradiance (mW/cm2)	Spots	Cumulative fluence (J/cm2)	Effective	Overall Level of Evidence	Guideline Category	Non-RCTs – study design (effective)
HSCT	P	Barasch 1995*	Hematol	Laser	632.8	25	1	40	31.25	18	18	Y			660 nm Bezinelli 2014 – 3 (Y) Bezinelli 2016 – 4 (Y) Jaguar 2007 – 4 (Y) Eduardo 2015 – 5 (Y) De Paula Eduardo 2015 – 3 (Y) Eduardo 2009 – 8 (Y) 685 nm IE & 830 nm EO Soto 2015^ – 3 (Y) Unknown wavelength Genot-Klastersky 2008 – 3 (Y)
HSCT	P	Cowen 1997	Hematol	Laser	632.8	60	1.5	10	150	75	112.5	Y			
HSCT	P	Antunes 2007	Hematol	Laser	660	46.7	4	16.7	238	105	415	Y			
HSCT	P	Schubert 2007 *	Hematol	Diode laser	780	70	2	1	2000	6	12	N			
HSCT	P	Schubert 2007*	Hematol	Diode laser	650	40	2	2	1000	6	12	Y			
HSCT	P	Khouri 2009	Hematol	Laser	660/780	25	6.3	10	630	-	-	Y	I	R	
HSCT	P														
HSCT	P	Silva 2011	Hematol	Laser	660	40	4	4	1000	80	320	Y			
HSCT	P	Silva 2015	Hematol	Laser	660	40	4	4	1000	80	320	Y			
HSCT	P														

Guideline relies on the “green” physical setting.
“Green” physical setting may vary greatly.

HSCT - Prevention

Cancer treatment modality	Aim	Author, Year	Cancer type	PBM source	Wave-length (nm)	Power (mW)	Fluence (J/cm2)	Time (sec.)	Irradiance (mW/cm2)	Spots	Cumulative fluence (J/cm2)	Effective	Overall Level of Evidence	Guideline Category	Non-RCTs – study design (effective)
HSCT	P	Barasch 1995*	Hematol	Laser	632.8	25	1	40	31.25	18	18	Y	I	R	660 nm Bezinelli 2014 – 3 (Y) Bezinelli 2016 – 4 (Y) Jaguar 2007 – 4 (Y) Eduardo 2015 – 5 (Y) De Paula Eduardo 2015 – 3 (Y) Eduardo 2009 – 8 (Y) 685 nm IE & 830 nm EO Soto 2015^ – 3 (Y) Unknown wavelength Genot-Klastersky 2008 – 3 (Y)
HSCT	P	Cowen 1997	Hematol	Laser	632.8	60	1.5	10	150	75	112.5	Y			
HSCT	P	Antunes 2007	Hematol	Laser	660	46.7	4	16.7	238	105	415	Y			
HSCT	P	Schubert 2007 *	Hematol	Diode laser	780	70	2	1	2000	6	12	N			
HSCT	P	Schubert 2007*	Hematol	Diode laser	650	40	2	2	1000	6	12	Y			
HSCT	P	Khouri 2009	Hematol	Laser	660/780	25	6.3	10	630	-	-	Y			
HSCT	P														
HSCT	P	Silva 2011	Hematol	Laser	660	40	4	4	1000	80	320	Y			
HSCT	P	Silva 2015	Hematol	Laser	660	40	4	4	1000	80	320	Y			
HSCT	P														

In case there is more than one effective, reproducible physical setting, it is advised to choose one of the settings, and to adhere to all the setting parameters reported in this clinical protocol.

Preliminary format of the guidelines

Guideline	Patient population	Protocol	Wavelength (nm)	Irradiance (mW/cm2)	Time (sec.)	Fluence (J/cm2)	Spot size (cm2)	Spots	Cumulative per session (J/cm2)	Comment
1	HSCT	1	650	1000	2	2.0	0.04	6	12	Schubert 2007
		2								
2	RT	1	632.8	24	125	3.0	1	12	36	Gautum 2015
3	RT-CT	1	632.8	27	125	3.3	1	12	36	Gautum 2013
		2	660	417	10	4.2	0.24	9	36	Antunes 2013
		3	660	625	10	6.3	0.04	69	420	Oton-Leite 2015

Section: Laser & Light Therapy

Phases:

4. Safety
    - Immediate adverse effect – for all papers
    - Long-term adverse effect – in the Discussion (Late Breaking News)

Summary

- Three sections
- Each section is unique in some way.
- The section's paper will extend on the details.
- The summary paper will present the bottom line.

Thank you

להוסיף את הטבלאות איפה שיש גיידליין

Glutamine

- Glutamine (parenteral) – HSCT – prevention
- Guideline: Recommendation against (LoE I)

- Glutamine (PO) – HSCT – prevention
- Guideline: No guideline possible (LoE III)

- Glutamine (PO) – RT-CT – prevention
- Guideline: suggestion (LoE II)

Glutamine

- Glutamine (topical) – RT-CT – prevention
- Glutamine (parenteral) – CT – prevention
- Glutamine (PO) – CT – prevention

- Guideline: No guideline possible

Elemental diet

- Elemental diet (PO) – HSCT – prevention
- Elemental diet (PO) – CT – prevention
- Elemental diet (PO - SS) – RT – prevention

- Guideline: No guideline possible

Methods

Unique considerations

- Laser & Light Therapy – additional data collected
  - Adequate level of reporting for the laser setting is required
  - Several options of sufficient level of laser setting reporting were defined
  - None-reproducible studies are excluded

1. 1+2+3+4 (i 1+2+3 ity; 2+4 *W*)
2. Fluence (energy density; J/cm^2)
3. Time per point (sec)
4. Irradiation (power density; mW/cm^2)

Methods

Unique considerations

- Pathogenesis
  - Single review per publication
  - Adjustment of the Review Form

- Seeds for our next projects
  - Embedded within this project

Glutamine

Route of Administration	Cancer	Treatment Modality	Indication	Author, Year	Effective	Overall Level of Evidence	Non-RCT studies
Topical	H&N	RT	P	Huang 2000	Y	III	
Parenteral	Hem	CT	P	Sornsuvit 2008	Y	III	Ward 2009 – 3 (N) Yildirim 2013 – 4 (N) *
PO	Solid ca.	CT	P	Peterson 2007	Y	II	Skubitz 1996 – 4 (Y) Rubio 1998 – 4 (Y)
				Anderson 1998b – 9762946	Y		

Zinc (systemic): HSCT – Prevention
Zinc (systemic): CT – Prevention
Zinc (topical): CT – Prevention
Guideline: No guideline possible

Route of Administration	Cancer	Treatment Modality	Indication	Author, Year	Effective	Overall Level of Evidence	Non-RCT studies
PO	Hem.	HSCT	P	Mansouri 2012	**N**	II	Hayashi 2014 – 6 (N)
PO	Hem. & solid ca.	CT	P	Arbabi-Kalati 2012	**N**	III	
Topical	Hem.	CT	P	Mehdipour 2011	**N**	III	

Elemental diet

Route of Administration	Cancer	Treatment Modality	Indication	Author, Year	Effective	Overall Level of Evidence	Non-RCT studies
Parenteral	Hematol	HSCT	P	Van Zaanen 1994	**N**	I	
PO	Hematol	HSCT	P	-	**N**	IV	Morishita 2016 – 4 (N)
PO	Solid ca.	CT	P	Tanaka 2016	**Y**	III	Ogata 2016 – 4 (Y)
SS	H&N	RT/RT-CT	P	-	**Y**	IV	Harada 2016 – 4 (Y)

Supersaturated CaPho – HSCT – Prevention

Supersaturated CaPho – HSCT and CT - Treatment

Supersaturated CaPho – RT-CT - Prevention

Guideline: No guideline possible

Route of Administration	Cancer	Treatment Modality	Indication	Author, Year	Effective	Overall Level of Evidence	Non-RCT studies
Topical	Hem.	HSCT	P	Papas 2003	Y	III	Wasko-Grabowska 2012 – 3 (Y) Wasko-Grabowska 2011 – 4 (N)
				Markiezicz 2012	Y		
				Svanberg 2015	N		
Topical	Hem. & solid	HSCT/CT	T	Raphael 2014	N	III	
Topical	H&N	RT-CT	P	Lambrecht 2013	N	III	Stokman 2012 – 3 (N)