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**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Cancer Type</th>
<th>Treatment Modality</th>
<th>Indication</th>
<th>Author, Year</th>
<th>Effective</th>
<th>Overall Level of Evidence</th>
<th>Non-RCT studies</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Epstein 1989[22]</td>
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<td></td>
<td>Jayachandran 2012 [23]</td>
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**Benzydamine (rinse): H&N – RT-CT - Prevention**  
**Guideline: Recommendation**

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

[ES1] The previous guideline limited it up to 50 Gy. I think it was based on the Epstein 2001 study. I found on page 880-881 a paragraph stating it was effective up to 50 GY. Please confirm.

If so, will you agree to change the guideline wording?

Please add for each non-RCT if it was effective (Y) or ineffective (N) after the study type. Example: "3 (Y)"

[ES2] Please check any of the papers that are RT-CT all along this table, and add this information (temporarily) in the table.

[ES3] In the Sheibani 2015 – only 42% were RT-CT. Please check any of the papers that are RT-CT all along this table, and add this information (temporarily) in the table.

[ES4] Based on this information we will know how to address it:

- Possibly change the title to "mix RT/RT-CT"
- Possibly changing to "suggestion" or even "no guideline possible" depending on how variable the population will be.

I think we should list separately systemic and topical administration. I changed the table accordingly.

[ES5]
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 swallow) – 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

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

• Chlorhexidine, CHX (vs. placebo; vs. an active agent)
Categories

• Oral care multi-agent combination protocols

• Professional care

• Patient education

• Normal saline

• Sodium bicarbonate

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

• Chlorhexidine, CHX (vs. placebo; vs. an active agent)
Categories

- Oral care multi-agent combination protocols
- Professional care
- Patient education
- Normal saline
- Sodium bicarbonate

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

- Chlorhexidine, CHX (vs. placebo; vs. an active agent)
### Oral care multi-agent combination protocols

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Population</th>
<th>Indication</th>
<th>RCTs Author, Year</th>
<th>Effective</th>
<th>Overall Level of Evidence</th>
<th>Non-RCT studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT +/- TBI/TLI</td>
<td>Hematol.</td>
<td>P</td>
<td>Kenny 1990</td>
<td>(\text{N})</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>H&amp;N</td>
<td>P</td>
<td>Shieh 1997</td>
<td>(\text{Y})</td>
<td>III</td>
<td>Janjan 1992 – 3((\text{Y}))</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kartin 2014</td>
<td>(\text{Y})</td>
<td></td>
<td></td>
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</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention Group</th>
<th>Control/ Comparative Group</th>
</tr>
</thead>
</table>
| 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**, 3 days/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

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Population</th>
<th>Indication</th>
<th>RCTs Author, Year</th>
<th>Effective</th>
<th>Overall Level of Evidence</th>
<th>Non-RCT studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>H&amp;N</td>
<td>P</td>
<td>Spijkervet 1989</td>
<td>N</td>
<td>III</td>
<td></td>
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<tr>
<td>CT</td>
<td>Hematol.</td>
<td>P</td>
<td>Djuric 2006</td>
<td>Y- Pain duration N- OM severity</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Solid ca.</td>
<td></td>
<td>Saito 2014</td>
<td>Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT &amp; CT</td>
<td>H&amp;N</td>
<td>P</td>
<td>Yonedda 2007</td>
<td>Y</td>
<td>III</td>
<td>Kubota 2015 – 3(Y), Yokata 2016 - 4(N)</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Population</th>
<th>Indication</th>
<th>RCTs Author, Year</th>
<th>Effective</th>
<th>Overall Level of Evidence</th>
<th>Non-RCT studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT</td>
<td>H&amp;N</td>
<td>P</td>
<td>Spijkervet 1989</td>
<td>N</td>
<td>III</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hematol. &amp; solid ca.</td>
<td></td>
<td>Ferretti 1990</td>
<td>N</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not stated (Likely H&amp;N)</td>
<td></td>
<td>Foote 1994</td>
<td>N</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

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
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   • Consultation with a physicist and a laser researcher
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3. Concluding clinical guidelines
   • Combination of evidence about clinical efficacy and reproducible laser setting parameters.
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/cm\(^2\)) \times 1000 / time (sec)

Data reported:
• Power density = 583 mW/cm\(^2\)
• Fluence = 72 J/cm\(^2\)
• Time = 54 sec

Calculated:
• 72 \times 1000 / 54 = 1333 mW/cm\(^2\)
• Not valid reporting
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.
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/cm²) = 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,

<table>
<thead>
<tr>
<th>Wavelength (nm)</th>
<th>Power (mW)</th>
<th>Fluence (J/cm²)</th>
<th>Time (sec.)</th>
<th>Irradiance (mW/cm²)</th>
<th>Spots</th>
<th>Cumulative fluence (J/cm²)</th>
<th>Effective</th>
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<tbody>
<tr>
<td>650</td>
<td>40</td>
<td>2</td>
<td>2</td>
<td>1000</td>
<td>6</td>
<td>12</td>
<td>Y</td>
</tr>
<tr>
<td>632.8</td>
<td>60</td>
<td>1.5</td>
<td>10</td>
<td>150</td>
<td>75</td>
<td>112.5</td>
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</table>

Evidence clustered by cancer therapy modality

Major flaws, power analysis + physical reproducibility

No major flaws + powered + physical setting is valid = Guideline
## HSCT - Prevention

<table>
<thead>
<tr>
<th>Cancer treatment modality</th>
<th>Aim</th>
<th>Author, Year</th>
<th>Cancer type</th>
<th>PBM source</th>
<th>Wave-length (nm)</th>
<th>Power (mW)</th>
<th>Fluence (J/cm²)</th>
<th>Time (sec)</th>
<th>Irradiance (mW/cm²)</th>
<th>Spots</th>
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<th>Effective</th>
<th>Overall Level of Evidence</th>
<th>Guideline Category</th>
<th>Non-RCTs – study design (effective)</th>
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<tbody>
<tr>
<td>HSCT</td>
<td>P</td>
<td>Cowen 1997</td>
<td>Hematol</td>
<td>Laser</td>
<td>632.8</td>
<td>60</td>
<td>1.5</td>
<td>10</td>
<td>150</td>
<td>75</td>
<td>112.5</td>
<td>Y</td>
<td>I</td>
<td>R</td>
<td>685 nm IE &amp; 830 nm EO Soto 2015^ – 3 (Y) Unknown wavelength Genot-Klasterinky 2008 – 3 (Y)</td>
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<td>46.7</td>
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<td>R</td>
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<tr>
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<td>P</td>
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<td>Hematol</td>
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<td>70</td>
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<td>1</td>
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<td>P</td>
<td>Schubert 2007*</td>
<td>Hematol</td>
<td>Diode laser</td>
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<td>40</td>
<td>2</td>
<td>2</td>
<td>1000</td>
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<td>R</td>
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<td>80</td>
<td>320</td>
<td>Y</td>
<td>I</td>
<td>R</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Patient population</th>
<th>Protocol</th>
<th>Wavelength (nm)</th>
<th>Irradiance (mW/cm²)</th>
<th>Time (sec.)</th>
<th>Fluence (J/cm²)</th>
<th>Spot size (cm²)</th>
<th>Spots</th>
<th>Cumulative per session (J/cm²)</th>
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<tbody>
<tr>
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<td>1000</td>
<td>2</td>
<td>2.0</td>
<td>0.04</td>
<td>6</td>
<td>12</td>
<td>Schubert 2007</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
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<td>27</td>
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<td>69</td>
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</table>

1. HSCT 1: Wavelength (650 nm), Irradiance (1000 mW/cm²), Time (2 sec.), Fluence (2.0 J/cm²), Spot size (0.04 cm²), Spots (6), Cumulative per session (12 J/cm²). Schubert 2007
2. RT 1: Wavelength (632.8 nm), Irradiance (24 mW/cm²), Time (125 sec.), Fluence (3.0 J/cm²), Spot size (1 cm²), Spots (1), Cumulative per session (36 J/cm²). Gautum 2015
3. RT-CT 1: Wavelength (632.8 nm), Irradiance (27 mW/cm²), Time (125 sec.), Fluence (3.3 J/cm²), Spot size (1 cm²), Spots (1), Cumulative per session (36 J/cm²). Gautum 2013
4. RT-CT 2: Wavelength (660 nm), Irradiance (417 mW/cm²), Time (10 sec.), Fluence (4.2 J/cm²), Spot size (0.24 cm²), Spots (9), Cumulative per session (36 J/cm²). Antunes 2013
5. RT-CT 3: Wavelength (660 nm), Irradiance (625 mW/cm²), Time (10 sec.), Fluence (6.3 J/cm²), Spot size (0.04 cm²), Spots (69), Cumulative per session (420 J/cm²). 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
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. Power (intensity; mW)
2. Fluence (energy density; J/cm²)
3. Time per point (sec)
4. Irradiation (power density; mW/cm²)
Methods

Unique considerations

• **Pathogenesis**
  • Single review per publication
  • Adjustment of the Review Form

• **Seeds for our next projects**
  • Embedded within this project
## Glutamine

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<thead>
<tr>
<th>Route of Administration</th>
<th>Cancer</th>
<th>Treatment Modality</th>
<th>Indication</th>
<th>Author, Year</th>
<th>Effective</th>
<th>Overall Level of Evidence</th>
<th>Non-RCT studies</th>
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## Elemental diet

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Supersaturated CaPho – HSCT – Prevention
Supersaturated CaPho – HSCT and CT - Treatment
Supersaturated CaPho – RT-CT - Prevention

Guideline: No guideline possible

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