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SPECIAL ARTICLE

Systematic review of laser and other light therapy for the management of oral mucositis in cancer patients

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Abstract
Background The aim of this study was to review the available literature and define clinical practice guidelines for the use of laser and other light therapies for the prevention and treatment of oral mucositis.

Methods A systematic review was conducted by the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology. The body of evidence for each intervention, in each cancer treatment setting, was assigned an evidence level. Based on

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the evidence level, one of the following three guideline determinations was possible: recommendation, suggestion, and no guideline possible.
Results A new recommendation was made for low-level laser (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 (2 s/point)) for the prevention of oral mucositis in adult patients receiving hematopoietic stem cell transplantation conditioned with high-dose chemotherapy, with or without total body irradiation. A new suggestion was made for low-level laser (wavelength around 632.8 nm) for the prevention of oral mucositis in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer. No guideline was possible in other populations and for other light sources due to insufficient evidence.
Conclusions The increasing evidence in favor of low-level laser therapy allowed for the development of two new guidelines supporting this modality in the populations listed above. Evidence for other populations was also generally encouraging over a range of wavelengths and intensities. However, additional well-designed research is needed to evaluate the efficacy of laser and other light therapies in various cancer treatment settings.

Keywords Oral mucositis · Stomatitis · Laser therapy · LLLT · LED · Oral complications of cancer therapy · Mucositis prevention · Mucositis treatment

Introduction

This manuscript is part of a collaborative effort of the Mucositis Study Group of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) to update the existing guidelines for the prevention and treatment of oral mucositis (OM) in cancer patients. The original and last update of the guidelines in 2004 and 2007, respectively [1, 2], reviewed the various therapies for mucositis, including the use of low-level laser therapy (LLLT) [3].

It is known that radiation at certain wavelengths can be beneficial to cells and tissues [4], but there is uncertainty on how this happens. Phototherapy, including LLLT, is based on the interaction of light at low-energy density, a few joules per square centimeter, with cells and tissues without the generation of thermal effects. This type of therapy is believed to promote photochemical, photophysical, and photobiological effects in cells and tissues, without causing temperature rise above 98 °F. It is believed that the biomodulation effect on cells and tissues occurs due to the absorption of the light energy by endogenous photoreceptors [4]. In 1989, a review of several in vitro studies [5] revealed that primary photoactivated receptors are components of the cellular respiratory chain. The activation of these receptors could lead to the stimulation or inhibition of the cellular metabolism, depending on the energy dose of light. Low-energy doses could regulate the production of reactive oxygen species. Visible light can lead to photochemical changes in the photoreceptors in the mitochondria, altering cell metabolism and producing a transduction effect in other cell components (biomodulation effect) [5]. Others suggest that this effect is due to photophysical changes on the Ca++ channels in the cell membrane [6]. Studies in animal models of oral mucositis have demonstrated that LLLT can promote wound healing as well as have an anti-inflammatory effect, evidenced by a reduction in neutrophil infiltrate and cyclooxygenase-2 expression [7, 8].

Several laser parameters that could alter tissue biology include wavelength (in nanometer), power (in milliwatt), amount of energy delivered to the tissues (in joules per square centimeter), time (in seconds), and the rate of energy delivered into tissues (in milliwatts per square centimeter) [9]. The use of these laser parameters has to be adjusted based on the biological process one is aiming to modulate. Oral mucositis is a complex pathobiological process that involves several epithelial and subepithelial tissue interactions with chemotherapy agents and/or radiation therapy [10]. Thus, the goal is to determine how to best utilize laser parameters to obtain the best biomodulation of tissue reactions.

At the time of the last mucositis guidelines review by the Mucositis Study Group of MASCC/ISOO [3], studies testing laser therapy were few. The panel noted that LLLT requires expensive equipment and specialized training. Because of inter-operator variability, clinical trials are difficult to conduct, and their results are difficult to compare; nevertheless, the panel was encouraged by the accumulating evidence in support of LLLT and suggested that, for centers able to support the necessary technology and training, LLLT be used to attempt to reduce the incidence of oral mucositis and its associated pain in patients receiving high-dose chemotherapy or chemoradiotherapy before hematopoietic stem cell transplant (HSCT).

As part of a comprehensive update of the MASCC/ISOO clinical practice guidelines for mucositis, the aim of this project was to systematically review the available literature and define evidence-based clinical practice guidelines for the use of laser and other light therapy devices for the prevention and treatment of OM.

Methods

The methods used in this systematic review are described in detail in Bowen et al. and Elad et al., elsewhere in this issue.

Briefly, a literature search for relevant papers indexed before 31 December 2010 was conducted using OVID/MEDLINE, with papers selected for review based on defined inclusion and exclusion criteria.

Selected papers were reviewed by two independent expert reviewers and data were extracted using a standard electronic form. Studies were scored for their level of evidence based on Somerfield criteria [11] and flaws were listed according to Hadorn criteria [12]. A well-designed study was defined as a study with no major flaws per the Hadorn criteria [12].

Findings from the reviewed studies were integrated into guidelines based on the overall level of evidence for laser and other light therapy agents. Guidelines were classified into three types: recommendation, suggestion, and no guideline possible. Guidelines were separated based on (1) the aim of the intervention (prevention or treatment of mucositis), (2) the treatment modality (radiotherapy, chemotherapy, chemoradiotherapy, or high-dose conditioning therapy for hematopoietic stem cell transplant), and (3) the route of administration of the intervention, when applicable.

The list of intervention keywords used for the literature search of this section included oral mucositis or stomatitis AND lasers, laser, LLLT, low level laser therapy, light therapy, phototherapy, low-level laser, LED, light-emitting diode, diode, visible light, He-Ne, InGaAlP, GaAlAs, InGaAs, CO2, and infra-red.

Results

The literature search identified a total of 692 papers from which a total of 24 clinical trials were included for final review [9, 13–35]. The literature review process can be seen in Fig. 1.

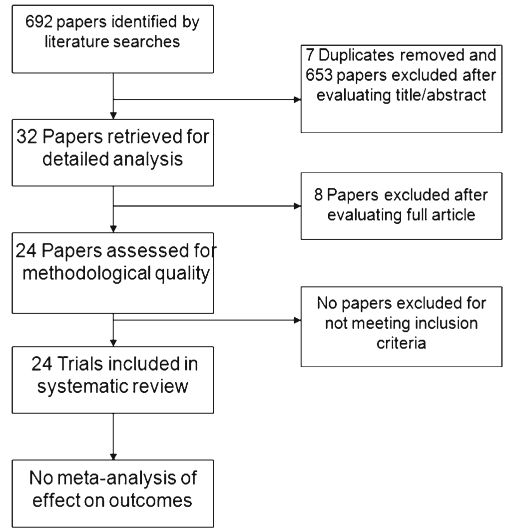

Fig. 1 Literature search: Flow of papers from initial identification through final selection for review

Oral mucositis in patients undergoing hematopoietic stem cell transplant, with or without total body irradiation

A recommendation was possible for laser therapy in the wavelength around 650 nm, the intensity of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2 (2 s/point; personal communication) for the prevention of oral mucositis in HSCT. This guideline is based on the combination of one well-designed randomized clinical trial with no major flaws [9] together with a series of studies reporting positive results with laser in a similar range of wavelength which were classified at a lower level of evidence.

The pivotal trial evaluated the efficacy of two different low-level gallium aluminum arsenide diode lasers, 650 and 780 nm wavelengths in the prevention of oral mucositis in HSCT patients conditioned with chemotherapy or chemoradiotherapy [9]. Patients with clinically normal oral mucosa received intraoral laser irradiation in several areas of the mucosa, with energy densities of 2 J/cm^2. Because of the preventive nature of the study, laser treatment began on the first day of the conditioning and continued through day +2 post-HSCT. It was observed that the severity of OM score in patients treated with the 650-nm laser was reduced, compared with placebo and the 780-nm laser groups (p=0.06). Of importance is the fact that patients in the 650-nm group statistically significantly likely received total body irradiation (TBI) thus a more aggressive therapy protocol. An adjusted statistical test for TBI showed that the difference in mucositis severity on day 11 post-HSCT was statistically significant (p=0.03). Laser therapy was well-tolerated and no adverse events developed.

In contrast to the above-mentioned guideline, no guideline was possible for laser as a treatment of OM in HSCT patients. Two studies with mixed cancer populations [20, 21] were insufficient to allow for any guideline.

Two non-laser light-therapy devices were reported in the literature for the prevention of OM in HSCT patient population: light-emitting diode (LED) and broad band visible light therapy [21, 22]. As to LED, there are accumulating data showing that there is no difference in the interaction of a laser and a LED with the human tissue [36–40]. These studies showed positive effects in prevention and treatment of oral mucositis but represent initial investigations of new light technologies, and with the available information no guideline was possible.

Radiotherapy-induced OM

A suggestion was possible for laser therapy in the prevention of OM in patients undergoing radiotherapy, without concomitant chemotherapy, for head and neck cancer. This guideline is based on three studies showing positive results with laser therapy in the wavelength of 632 nm [24–26]. However, all three studies had major flaws per the Hadorn criteria, which did not allow for a recommendation.

Radiochemotherapy-induced OM

No guideline was possible for laser therapy in the prevention or treatment of oral mucositis in patients treated with a combined protocol of radiochemotherapy for head and neck cancer. Studies were inconsistent in demonstrating the effectiveness of laser therapy in this population [27–29]. In addition, major flaws in study design reduced the overall level of evidence to IV.

Chemotherapy-induced oral mucositis

Studies examining the effects of laser therapy in this population generally reported positive results. However, due to a low overall level of evidence (IV) and varying laser parameters, no guideline was possible for this category either for the prevention or treatment of mucositis using laser therapy or LED.

Discussion

This systematic review confirmed that the number of clinical trials assessing the use of laser therapy in the prevention and treatment of oral mucositis is growing. It is important to keep in mind that the data presented in this review result from the use of a variety of low-level laser and other light devices that operate in different wavelengths and are applied to tissues using a variety of protocols. Most devices were within the range considered to be low-level laser (10–200 mW) (Table 1). Laser application protocols vary greatly and, therefore, conclusions cannot be applied separately for each of the individual laser devices.

Based on the current scientific information, the panel was able to reach the following decision: “The panel recommends that, for centers able to support the necessary technology and training, LLLT be used to prevent oral mucositis, in HSCT patients receiving high-dose chemotherapy with or without TBI.” The best evidence supports the following protocol: 650 nm, with the intensity of 40 mW, and each square centimeter treated with the required time to a tissue energy dose of 2 J/cm^2 (2 s/point) to the oral mucosa [9]. This represents a significant change from our previous guidelines in which the use of laser therapy was only a suggestion in HSCT patients. At that time, it had been determined that new evidence from additional randomized trials was necessary before a recommendation could be made [1, 2]. This new recommendation reflects the growing interest in the use of these devices in oral mucositis.

Our findings are generally consistent with two Cochrane meta-analyses that evaluated the prevention and treatment of oral mucositis with LLLT. The Cochrane *prevention* meta-analysis [41] analyzed two studies [16, 18] that together showed an 80 % reduction in the incidence of severe mucositis in HSCT. It concluded that overall there is weak evidence from two small studies at some risk of bias that low-energy laser application may be beneficial in preventing severe mucositis. In addition, the Cochrane *treatment* meta-analysis [42] analyzed two additional studies [20, 23] with a combined statistically significant benefit for LLLT in oral mucositis in mostly HSCT patients [12]. It concluded that there is limited evidence from two small trials that low-level laser treatment reduces the severity of mucositis.

As a suggestion for future research in the field of OM, several aspects of research design should be considered.

- Information already known about laser parameters that is effective should be taken into account. Future studies should examine the effect of altering these laser parameters in different patient populations.
- Major flaws should be avoided when designing a new study (for example, see the Hadorn criteria [12]). Some of the major flaws observed in the studies reviewed in the present study included lack of a well-defined randomization, not using a placebo group, no double-blinding of both the investigator and the patient, a clear definition of possible confounders that could affect the response to laser therapy, and not using a valid tool for mucositis grading. In addition, laser parameters used were often incompletely described, which limits reproducibility.
- Consider further assessing the effects of phototherapy in an animal model of OM with a focus on elements in the pathobiological process of OM.
- Oral mucositis affects various tissue layers (surface epithelium and subepithelial). Since laser wavelength can affect depth of tissue penetrance, perhaps the combined use of both short and long wavelengths could provide a synergistic effect on mucositis outcomes.
- The newly available blue LED has potential for the management of OM, and research is warranted based on the known effects of this light therapy in wound healing [43].

To emphasize the growing body of evidence in favor of LLLT in OM, several relevant late-breaking publications have been added to the laser-oral mucositis literature since the time we completed the literature search in December 2010. A systematic review with meta-analysis concluded that there is consistent evidence from small high-quality studies (mostly also included in the present review) that

Table 1 Data available in the literature

Indication	Laser type	Type of light therapy	Wavelength (nm)	Intensity (mW)[a]	Energy density (J/cm^2)[a]	Time (s)[a]	Power density (mW/cm^2)[a]	Laser setting–additional information	Route of application	Treatment modality	Patient population	Reference (author, year)	Effectiveness	Overall level of evidence	Guideline	Comments
P	HeNe	Laser	632.8	60	1.5	10			IO	HSCT w TBI	Adult	Cowen 1997 [13]	Y	II	Recommendation	He-Ne laser decreases severity but not incidence of OM
	HeNe	Laser	632.8	25	1	40			IO	HSCT w/wo TBI	Adult	Barasch 1995 [14]	Y			He-Ne laser decreases severity but not incidence of OM
	GaAlAs	Laser diode	660/780	40	2	2/pnt		For 40 mW, 2 s/point (0.08 J/point); for 60 mW, 1 s/point	IO	HSCT w/wo TBI	Adult	Schubert 2007 [9]	Y			Diode 650 nm 2 J/cm^2 LLLT reduces OM severity
				60	2	1/pnt		2 J/cm2 (0.8 J/point) (personal communication)								
	GaAlAs	Laser diode	660	10	2.5	10			IO	HSCT w/wo TBI	Adult	Jaguar 2007 [15]	Y			Laser increased time of OM appearance, reduced time of pain and morphine use
	GaAlAs	Laser diode	780	60	4	NS			IO	Mixed: HSCT* & CT	Pediatric	Cruz 2007 [16]	N			No evidence of benefit from the prophylactic use of low-energy laser in patients with cancer on chemotherapy who received optimal dental and oral care.
	InGaAIP	Laser diode	660	40	4	NS			IO	HSCT w/woTBI	Mixed	Eduardo 2009 [17]	Y			OM measured by WHO scale was maintained at grades I and II in 22/30 patients, grade III in 7 and IV in 1, in HSCT patients receiving high-dose CT
	InGaAlP	Laser diode	660	50	4	16.7			IO	HSCT w/woTBI	Adults	Antunes 2007 [18]	Y			Preventive use of laser in HSCT patients is a powerful instrument in reducing the incidence of OM
	InGaAlP/GaAlAs	Laser diode	660/780	25	6.3	10			IO	Mixed: HSCT w/wo TBI and CT	Adults	Khouri 2009 [19]	Y			LLLT—lower frequency, progression, and severity of OM
T	GaAlAs	Laser diode	830	100	4	–[b]			IO	Mixed: HSCT[c] and CT	Pediatric	Kuhn 2009 [20]	Y	III	No guideline possible	Encourage pediatric oncologists to use laser therapy as first-line option for children with chemotherapy-induced OM.
P	LED	Light-emitting diode	670		4	71	56		EO	HSCT w/woTBI	Mixed	Whelan 2002 [21]	Y	III	No guideline possible	Although more studies are needed, LED therapy appears useful in the prevention of OM in pediatric HSCT patients

Table 1 (continued)

Indication	Laser type	Type of light therapy	Wavelength (nm)	Intensity (mW)[a]	Energy density (J/cm^2)[a]	Time (s)[a]	Power density (mW/cm^2)[a]	Laser setting–additional information	Route of application	Treatment modality	Patient population	Reference (author, year)	Effectiveness	Overall level of evidence	Guideline	Comments
P	Visible light	Visible light	400–1,200		9–18	45–90	165–200		IO	HSCT[c]	Adult	Elad 2006 [22]	Y	III	No guideline possible	Broadband visible light therapy is safe and effective in the prevention of oral mucositis in HSCT patients.
T	NS		NS	100 50, 250, 500	2	33		100 mW for “laser”; 50, 250, 500 mW for “infra-red”	IO	HSCT w/wo TBI	Adult	Genot-Klastersky 2008 [23]	Y	III	No guideline possible	Therapeutic laser therapy is beneficial for patients undergoing HSCT in delaying the development of OM grade 3.
P	HeNe	Laser	632.8	60	2	3			IO	RT of H&N	Adult	Bensadoun 1999 [24]	Y	III	suggestion	He-Ne effective in preventing RT OM
	HeNe	Laser	632.8	10	1.8	180			IO	RT of H&N	Adult	Arun Maiya 2006 [25]	Y			OM healing time reduced Effective for P and T
	HeNe	Laser	632.8	10	1.8	–[b]			EO and IO	RT of H&N	Adult	Arora 2008 [26]	Y			Significant reduction of OM grade in study group
P	InGaAlP	Laser diode	685	35	1.1	32			IO	CT/RT of H&N	Adult	Kelner 2007 [27]	N	IV	No guideline possible	LLLT and chlorhexidine have similar effects
	InGaAlP	Laser diode	660	30	2	NS			IO	CT/RT of H&N	Adult	Zanin 2010 [28]	Y			Improves quality of life and decreases incidence of OM in patients with H&N cancer treated with CT and RT
	NS		830	60	12	NS			IO	CT/RT of H&N	Adult	Lima 2010 [29]	Y			Delayed appearance of OM. Similar results for LLLT and aluminum hydroxide
T	GaAlAs/ InGaAlP	Laser diode	808/660	40	6	6			IO	CT/RT of H&N	Mixed	Simoes 2009 [30]	N	IV	No guideline possible	Laser applied 3/week maintains oral mucositis to grades 1 and 2. Not enough information to allow for a conclusion
P	GaAlAs	Laser diode	685	35	70	54		35 mW; 2 J/point 70 J/cm^2, 54 s	IO	CT	Mixed	Abramoff 2008 [31]	Y	IV	No guideline possible	LLLT has both a preventive and a therapeutic role in those prone to develop OM
	NS		NS	100 50, 250, 500	2	33		100 mW for “laser”; 50, 250, 500 mW for “infra-red”	IO	CT	Adult	Genot-Klastersky 2008 [23]	Y			Preventive laser therapy in beneficial in reducing the occurrence and intensity of OM in patients with solid tumors who have had previous mucositis
T	NS		830	45–50	0.7–0.8	600–1,800		–[d]	IO	CT	Adult	Wong 2002 [32]	Y	IV	No guideline possible	Reduced incidence and severity of OM
	GaAlAs		685	35	70	54		2 J/point	IO	CT	Mixed	Abramoff 2008 [31]	Y			Pain relief and possible decrease in the severity of OM
	InGaAlP		660/830	100	2	NS			EO	CT	Pediatric	Moraes 2009 [33]	Y			Both 830 and 660 nm lasers improved healing of oral mucositis with extraoral application in pediatric patients with established oral mucositis
	AsGaAl	Laser diode	830	250	35	NS			IO	CT	Adult	Nes 2007	Y			Study aimed at the analgesic effect only

Table 1 (continued)

Indication	Laser type	Type of light therapy	Wavelength (nm)	Intensity (mW)[a]	Energy density (J/cm^2)[a]	Time (s)[a]	Power density (mW/cm^2)[a]	Laser setting–additional information	Route of application	Treatment modality	Patient population	Reference (author, year)	Effectiveness	Overall level of evidence	Guideline	Comments
T	LED		645±15	7.8	0.99	300		–[d]	IO	CT	Adult	Corti 2006 [34]	Y	V	No guideline possible	The median healing time was 1.7 and in 7 L+ patients, was shorter than in the L group. The healing rate increased
T	NS		660	30	2	66			IO	Mixed: RT of H&N and CT	Mixed	Sandoval 2003 [35]	Y			Beneficial effects on the management of oral mucositis, improving the quality of life

Pediatric <17 years old

NS not specified, *P* prevention, *T* treatment, *IO* intraoral, *EO* extraoral, *HSCT* hematopoietic stem cell transplantation, *w* with, *wo* without, *TBI* total body irradiation, *CT* chemotherapy, *H&N* head and neck, *RT* radiotherapy, *Y* yes, *N* no, *pnt* point

[a] Setting is expressed as one of two options: (1) intensity (in milliwatt), energy density (in joules per square centimeter), time (in seconds); (2) power density (in milliwatts per square centimeter), energy density (in joules per square centimeter)

[b] The methods specify "The treatment time for each application point was given by the equation t(s) = energy (J/cm^2) × surface area (cm^2)/power (W)"; however, the surface area was not reported neither stated it was measured. With two missing parameters in this formula (time and surface), it is impossible to extract the data needed to reproduce the clinical setting

[c] Time was specified per patient session and not per point of application or per square centimeter. This description is insufficient to apply it for patients with other surface area

[d] It is not specified whether conditioning regimen included TBI or not

red and infrared LLLT can partly prevent development of cancer therapy-induced OM. It indicated that LLLT significantly reduces pain, severity, and duration of symptoms in patients with OM [44]. Additional data from a trial with near-infrared light-emitting diodes applied extraorally in children and adults with hematological malignancies and solid tumors treated with HSCT demonstrated that the technology can significantly reduce patient-reported pain [45]. A recent randomized study in patients with malignancies treated with HSCT confirmed that oral mucositis incidence and severity can be reduced with LLLT [46].

Late-breaking studies also showed positive outcomes on the prevention and treatment of oral mucositis in head and neck cancer populations being treated with radiation therapy [47], and in prevention of oral mucositis in head and neck cancer populations being treated with concurrent chemoradiation, indicating that this technology seems to be effective in controlling the appearance and severity of OM, its associated pain, and it can also have beneficial effects on quality of life [46, 48, 49].

Because of the variety of laser devices and the variation in individual protocols of laser and other light applications in oral mucositis, it is important to keep in mind that the results of each individual study apply exclusively to the cancer population studied, the wavelength of the laser device, and the settings utilized in that particular study. One additional issue that might play a role in the appearance and duration of OM is the absolute neutropenia observed in cancer populations treated with myelosuppressive therapies [50]. This confounder has not been evaluated in the majority of the trials and should be included in future investigations of the applicability of LLLT in OM prevention, treatment, and associated pain.

The mechanisms by which lasers promote beneficial effects in OM are not well understood and extrapolated from experimental models. For instance, lasers are forms of coherent light emission. New technologies like LEDs and other non-coherent light waves can also be absorbed by tissue chromophores and promote biological effects. From the data available in the literature (Table 1), it seems that all effective light therapy devices work in similar wavelength bands concentrating around peaks in 650, 780, and 830 nm. The 650- and 780-nm lasers fall within the "red" range and the 830-nm laser falls within the "near infra-red" range. It is uncertain to what extent the difference in the wavelength of the laser devices is meaningful in terms of light–tissue interaction. Small difference in wavelength, for example 650 vs. 632.8 nm may have negligible impact on the clinical outcome; however, larger differences may have a clinical impact (for example 650 vs. 780 nm). In Schubert et al. [9], the wavelength of 650-nm laser produced better clinical results in the prevention of oral mucositis than the 780-nm laser. Although there is now evidence in the literature suggesting that lasers with wavelengths varying between 632 and 830 nm can have beneficial effects on preventing and treating oral mucositis, no specific protocols that investigated other parameters such as tissue fluency (energy density), ideal time of laser application, variations in cancer type, and cancer treatment regimens are available. It should be noted that there are no studies assessing the effectiveness of laser or other type of light source in any light range except for the red or near-infrared range.

With the advancement of the technology, the early high-pricing laser-emitting devices have been reduced considerably, making the technology readily available. Education and training of staff is another factor that must be considered when using LLLT. Most of the protocols studied require daily and long applications. However, based on the accumulating evidence, LLLT has the potential to become a routine practice in the prevention and treatment of oral mucositis and its associated pain

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