

## *Dental management in the Intensive Care Unit in the treatment of toxic epidermal necrolysis associated with phenytoin: case report*

### *Manejo odontológico na Unidade de Terapia Intensiva no tratamento da necrólise epidérmica tóxica associada a fenitoína: relato de caso*

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#### **ABSTRACT**

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are adverse reactions, usually medicine-related, in which extensive and painful mucocutaneous lesions are formed. Oral lesions are characterized by the presence of erosions and ulcers. The treatment usually requires intensive care in a hospital setting, where the Dentist is essential in the multidisciplinary team, as he will act in the treatment of oral lesions. In this article, a 26-year-old female patient was reported, who presented TEN-compatible mucocutaneous lesions associated with the drug Phenytoin and required admission to a Teaching Hospital. The treatment consisted of the immediate suspension of the Phenytoin use and systemic therapy with corticosteroids and immunosuppressants. Oral lesions were monitored by the hospital dentistry team. The procedures adopted were: oral hygiene with 0.12% non-alcoholic Chlorhexidine Digluconate solution, hydration of the oral tissue with an essential fatty acid, application of frozen chamomile tea, and prescription of topical Triamcinolone Acetonide. Also, low-level laser therapy sessions (red and infrared) were performed. Oral lesions evolved with significant improvement. In this case, the importance of the Dentist in the multi-professional team is demonstrated. Although there is no protocol, the procedures used in the present case can be an alternative to therapies used in SSJ and TEN oral lesions.

**Indexing terms:** Drug-related side effects and adverse reactions. Oral manifestations. Stevens-Johnson Syndrome.

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## RESUMO

A Síndrome de Stevens Johnson (SSJ) e a Necrólise Epidérmica Tóxica (NET) são reações adversas, geralmente medicamentosas. Na pele, formam-se máculas que se tornam pápulas, vesículas e bolhas, além de eritema extenso e desprendimento da epiderme. As lesões bucais caracterizam-se pela presença de erosões e úlceras dolorosas. O tratamento geralmente é realizado em âmbito hospitalar, com necessidade de cuidados intensivos, onde o Cirurgião-dentista é fundamental na equipe multiprofissional, pois atuará na terapêutica das lesões bucais. Neste artigo foi relatado o caso de uma paciente do sexo feminino, de 26 anos, a qual apresentou lesões mucocutâneas compatíveis com NET associadas ao medicamento Fenitoína e necessitou de internamento em um Hospital Universitário. O tratamento realizado foi a suspensão imediata do fármaco desencadeador, além de terapia sistêmica com corticóide e imunossupressor. As lesões bucais foram acompanhadas pela equipe de odontologia hospitalar. As condutas adotadas foram: higiene bucal com solução de Digluconato de Clorexidina 0,12% não alcoólica, hidratação da mucosa bucal com Ácido Graxo Essencial, aplicação de rasps de chá de gelo de camomila e prescrição de Triancinolona Acetonida tópica. Além disso, foram realizadas sessões de laserterapia de baixa intensidade (vermelho e infravermelho). As lesões bucais evoluíram com melhora significativa. A paciente permaneceu internada durante 22 dias, sendo 12 em Unidade de Terapia Intensiva. Este caso demonstra a importância do Cirurgião-dentista na equipe multiprofissional. Apesar de não haver um protocolo para as lesões bucais, as condutas utilizadas no presente caso podem ser uma alternativa de terapêuticas utilizadas em lesões de SSJ e NET.

**Termos de indexação:** Efeitos colaterais e reações adversas relacionados a medicamentos. Manifestações bucais. Síndrome de Stevens-Johnson.

## INTRODUCTION

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe adverse situations, usually medicine-related, and phenytoin had already been documented as one of the triggering agents of these conditions [1].

The diagnosis is usually clinical, based on characteristic findings of the syndrome associated with the antecedent of any of the etiological factors already reported<sup>1</sup>. The clinical distinction between SJS and TEN is based on the characteristics and extension of cutaneous involvement. By definition, SJS affects up to 10% of the body surface, while in TEN, cutaneous involvement exceeds 30%; cases ranging from 10% to 30% are classified as mixed [2].

On the skin, macules are formed that later become papules, vesicles and blisters, associated or isolated, in addition to extensive erythema, and detachment of the epidermis [2].

Oral lesions are characterized by the presence of erosions and ulcers. They are painful and often limit mouth opening, hinder speech, swallowing, and oral hygiene. Therefore, the treatment of oral lesions is important to reduce pain, restore food intake and prevent secondary infections [3].

The treatment is usually provided in a hospital setting, requiring intensive care [3]. Currently, hospital treatment must be multi-professional and the Dentist can contribute to the diagnosis and treatment of oral lesions, improving the patient's general health and life quality. In hospital dentistry, early detection and control of oral lesions prevent local and systemic complications that may originate in the oral cavity [4].

Photobiomodulation is the term to define the wide range of laser applications using low-energy densities and your user indicates recurrent aphthous stomatitis, herpes infections, mucositis, and burning mouth syndrome [5]. The low-light laser therapy can be used with the adjuvant treatment for oral lesions of SJS [6,7]. Photobiomodulation, performed with infrared low-light laser, assists in the control of pain and inflammation. Different mechanisms have been proposed to explain the analgesic and inflammatory effects of photobiomodulation, but there are still gaps in the mechanisms underlying [8]. The current evidence supports that photobiomodulation effective in pain control resulting from oral mucositis and radiodermatitis and may also reduce the need for analgesics [9]. In addition, photobiomodulation therapy improves wound healing by inducing increases in mitotic activity, numbers of fibroblasts, collagen synthesis, and neovascularization [10].

Therefore, the article's purpose is to report the oral performance with the multidisciplinary team, in front of a patient with TEN, associated with the use of phenytoin, who remained hospitalized in a University Hospital.

## CASE REPORT

A 26-year-old female patient arrived at the Teaching Hospital, presenting: severe diffuse confluent rash; generalized and extensive lesions involving the skin and mucous. According to reports by family members, the patient had two tonic-clonic seizures, being medicated with Phenytoin (100mg, tablet, orally, every 8 hours).

After 15 (fifteen) days using Phenytoin, she developed edema in the buccal and cervical region and upper limbs. Did not report pain, but had a sporadic fever, up to 38.9°C (102,02°F). She was medicated at the hospital in her city with Benzylpenicillin Benzatin (could not inform about the form of application/concentration) and, posteriorly, progressed with a fever and pain worsening and increasing pain, skin rash, and eating difficulties, due to ulcers in the oropharynx region. Nine days after the initial symptoms, she was moved to the emergency department of the Teaching Hospital.

According to the clinical characteristics and lesions extent, the diagnostic was Toxic Epidermal Necrolysis (TEN), associated with the use of Phenytoin.

The patient was hospitalized, and Phenytoin's use was immediately suspended. She was medicated with analgesics, systemic corticosteroids (Hydrocortisone 100 mg, lyophilized powder, 8/8 hours, intravenously, for five days), anticoagulant (Sodium Enoxaparin 40mg, injection solution, subcutaneously).

Laboratory tests on the first day showed: increased quantitative determination of C-reactive protein: 21.3 mg/dL (reference: <0.5 mg/dL), with a decrease to 7 mg/dL and 1.3 mg/dL in the seventh and fourteenth day of hospitalization, respectively; increased dosage of creatinophosphokinase: 1,116.0U/L (reference: 26.0 to 140.0 U/L); increased dosage of glutamic-pyruvic transaminase (GPT): 31 U/L (reference: <30 U/L); increased dosage of glutamic oxalacetic transaminase (GOT): 56 U/L (reference: 14-36 U/L); increase in prothrombin time: 15.3 seconds (reference: 11.8 to 14.4 seconds); increasement in activated partial thromboplastin time: 45 seconds (reference: 31.3 to 43.3 seconds); decrease in creatinine dosage: 0.39 mg/dL (reference: 0.60 to 1.10 mg/dL) keeping values low on all hospitalization days.

The leukogram and erythrogram were within the reference values. The platelet count was 138,000/mm<sup>3</sup> (reference: 150,000 – 450,000mm<sup>3</sup>), returning to the reference values from the second day of hospitalization. The blood culture result was negative.

On the third day of hospitalization, the patient was moved to the Intensive Care Unit (ICU), due to hypotension and emesis with bloody content, with a reduction in hemoglobin dosage: 11g / dL (reference: 12.0 to 15.5 g / dL), causing a mild anemic condition.

The ICU treatment consisted of maintaining systemic corticosteroids (for 5 days) and immunosuppressants (Ciclosporin 200mg, tablet, 24/24 hours, orally, for 21 days, started after the end of systemic corticosteroids).

The hospital dentistry team held daily care. On physical examination, it was possible to verify skin lesions with the appearance of macules and reddish spots – some with bullous characteristics, with diffuse edges and a positive Nikolsky sign – reaching 94.5% of the body according to the SCORTEN scale, including upper limbs (as shown figure 1), extremities of lower limbs, face, trunk, thighs, buttocks, vulval and anal region, sparing only the scalp. In addition,



**Figure 1.** Presence of macules and reddish spots with blistering in some regions of the upper limbs.

there was the presence of facial edema and erythema in the ocular conjunctiva. The lips showed vesicular, bullous, and ulcerated lesions, compromising the entire extension (perioral tissues, vermillion and oral commissures), with the presence of active bleeding and an initial formation of hemorrhagic crusts, as shown in figure 2.



**Figure 2.** Presence of macules and stains of red color and the formation of bubbles. Presence of active bleeding in the lips and perioral region with formation of hemorrhagic crusts.

On intraoral examination, ulcerated lesions were found involving the entire oral mucosa, with active bleeding. The patient reported pain symptoms and feeding/swallowing difficulties.

The conduct adopted was the application of the oral hygiene protocol to avoid secondary infection, consisting of the use of 0.12% non-alcoholic Chlorhexidine Gluconate solution, 12/12 hours being applied with the aid of gauze and oral hygiene swab, carefully, due to the presence of intense painful symptoms during the manipulation of oral tissues. Lip and perioral hydration was performed with Essential Fatty Acid solution; prescription of topical corticosteroids (Triamcinolone 1mg/g, 8/8 hours, topically, for 7 days); cryotherapy with shavings of frozen chamomile tea the lesions and debridement of hemorrhagic crusts. At the end of each session, the patient reported a decrease in painful symptoms.

During the ICU stay, low-level laser therapy sessions were held (Whitening Laser II device, DMC brand) with red light (wavelength  $660 \text{ nm} \pm 10 \text{ nm}$ , power:  $100 \text{ mW} \pm 20\%$ , fluency 25 at  $45 \text{ J} / \text{cm}^2$ , dose 1J, with applications every 48 hours) and infrared (wavelength  $808 \text{ nm} \pm 10 \text{ nm}$ , power  $100 \text{ mW} \pm 20\%$ , fluency 50 to  $110 \text{ J} / \text{cm}^2$ , dose 2J, with applications every 48 hours while symptoms were reported), totaling six laser therapy sessions. The application was carried out in a punctually, with 1 cm of distance between the points. The patient reported a significant reduction of pain symptoms at the end of each session.

The improvement of oral lesions and pain symptoms occurred gradually and, after twelve days, there was an onset of repair of skin and mucosal lesions, as shown in figure 3.

After twenty-two days of hospitalization (twelve at the ICU), the patient has received a medical release. After fifteen days, she returned to the dental clinic, where a significant improvement was noted, however, with some persistent ulcers in the upper lip mucosa, without painful symptoms (figure 4). A new session of low-level laser therapy was performed with red light (wavelength  $660 \text{ nm} \pm 10 \text{ nm}$ , power:  $100 \text{ mW} \pm 20\%$ , fluency 25 to  $45 \text{ J} / \text{cm}^2$ , dose 1J, single application), in a punctual way, with 1 cm distance between points. After this procedure, the patient was instructed to return to the clinic of the University Hospital in case of a worsening of the clinical condition and to continue dental care at the basic health unit in her neighborhood.



**Figure 3.** Aspect of the face, lips, upper, and lower limbs after 12 days.



**Figure 4.** Appearance of lesions on the skin, lips and upper lip after 15 days of hospital.

## **DISCUSSION**

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe pharmacodermias, with low incidence, but high mortality [11].

The Phenytoin has already been described as one of the drugs that trigger SJS and TEN [1], and the risk of developing SJS with simple administration of this drug is more common at the beginning of the treatment. Also, for every 10,000 people, the risk of developing SJS / TEN is approximately 8.3 for this drug [3].

The basic pathogenesis is a late drug hypersensitivity reaction, due to the deposition of the complement and immunoglobulin (IgG) components in the dermo-epidermal junctions and around dermis small vessels, then the expression, by keratinocytes, of the human leukocyte antigen (HLA-DR), which is similar to other inflammatory skin disorders. TCD8+ cells recognize the major histocompatibility complex I (MHC-I) and trigger skin lesions in SJS [1].

The most common laboratory findings are leukocytosis and increased C-reactive protein (CRP) [11]. In this case report, the patient presented only an increase in CRP, justified by the presence of the inflammatory condition, but the absence of leukocytosis in the blood count, which can be justified by the absence of an infectious process associated with the patient's clinical condition. The treatment is usually performed in a hospital setting, requiring intensive care. It involves the immediate suspension of the triggering drug, volume and electrolyte replacement, use of gastric protectors, anticoagulants to prevent thromboembolism, and medication based on symptoms [3].

Attention should be paid to temperature control and infection signs. When the severity of immune-related adverse events justifies the inflammation reversal, systemic corticosteroids are used. Cyclosporine (immunosuppressive) is an option for steroid-refractory cases [12].

Specialized literature does not provide a protocol for the treatment of oral lesions arising from TEN. Oral hygiene with 0.12% non-alcoholic Chlorhexidine Gluconate solution was used to avoid secondary infections. The Chlorhexidine has high substantivity (remains in the oral cavity for approximately 12 hours) and has a broad action spectrum, being effective against bacteria and fungus [13]. Fatty acid essential was employed due to the hydration potential and the formation of a protective barrier, providing relief in painful symptoms [14].

The LASER (Light Amplification by Stimulated Emission of Radiation) with a wavelength close to 660 nm (red light) affects the most superficial tissues; the infrared (820, 940 nm), on the other hand, reach deeper layers and are effective in controlling pain. All the energy emanating from the laser is absorbed by a thin layer of adjacent tissue and from the point reached by the radiation, triggering the epithelial and fibroblast proliferation, as well as cellular and vascular changes. The occurrence of collagen and elastin production, contraction of the wound, increased phagocytosis by macrophages, and proliferation and activation of lymphocytes have also been observed, in addition to the tension force that consequently accelerates healing [10,15].

Despite the systemic medication for pain control, the patient complained of pain located in the oral region, due to ulcerations. In order to provide comfort to the patient and search results from analgesia and reduced healing time, photobiomodulation therapy was chosen. The pain intensity is generally more prevalent in the inflammatory phase during the first hours and days after the injury, and in most cases, the pain decreases as tissue repair processes begin. Through photobiomodulation therapy, the pain and inflammation modulation can occur, among other factors, by reducing the levels of PGE2, IL-1, and expression of COX-2 [16].

At the end of each low-high laser therapy session performed by the dental team, the patient reported improvement of the painful symptoms and, after six sessions, at 48-hour intervals, there was a significant improvement. Other case reports have shown similar results with the use of laser therapy in clinical conditions similar to those presented. Rocha et al reported a case of a 17-year-old female patient diagnosed with SJS associated with Lamotrigine, used to control epilepsy. After two weeks using the medication, presented lip edema, oral ulcers, fever, intense odynophagia, reduced food intake, difficulty in oral communication and oral hygiene. Laser therapy was used to treat oral lesions. The result was satisfactory and, after 5 sessions, there was complete remission of the oral lesions [6].

Simões et al reported a case of a 7-year-old male patient who developed SJS associated with the use of Phenobarbital, used for convulsions. The patient was admitted to the ICU with fever, mucocutaneous lesions, the oral ulcerative bleeding, crusts, and the presence of severe pain. Laser therapy was instituted for oral lesions and, after six sessions, there was a significant improvement, with photobiomodulation therapy being suggested as a new treatment modality for oral lesions of SJS / NET [7].

The Chamomile is used as a herbal medicine with analgesic and anti-inflammatory action. The combination of cryotherapy with herbal medicine showed positive results in the present case because, at the end of the sessions of this procedure, the patient reported improvement of the painful symptoms [17].

Oral lesions evolved with significant improvement with the therapies employed. In general, the prognosis is good and skin lesions generally do not leave scars, but mucosal lesions can cause contraction [1]. It is worth mentioning that the repair time of the lesions is long and can be reduced with the use of specific therapies.

## **CONCLUSION**

The presence of a properly prepared dentistry professional on the multi-professional team – at a hospital setting – is essential for the diagnosis and treatment of oral lesions caused by Steven-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Considering that some of the clinical manifestations of SJS and TEN are painful ulcers in the oral mucous membranes and that current studies demonstrate positive results on (i) the effectiveness of the use of 0.12%

non-alcoholic Chlorhexidine Gluconate in preventing secondary infections; and (ii) phytotherapeutic action of frozen chamomile tea for pain relief and inflammation; and (iii) photobiomodulation therapy with its action in tissue repair and pain control; it is inferred that the union of these therapeutic measures could be integrated in a new protocol for the treatment of oral lesions related to SJS and TEN.

## Collaborators

CNA Ruppel, conceptualization; visualization, writing – original draft; writing – review & editing. NCS Martins, MD Ferreira and L Camargo, conceptualization; writing – original draft. M Claudino: supervision, visualization, writing – review & editing. EB Campagnoli, conceptualization; project administration, supervision, visualization, writing – review & editing.

## REFERENCES

- Bulisani ACP, Sanches GD, Guimarães HP, Lopes RD, Vendrame LS, Lopes AC. Síndrome de Stevens-Johnson e Necrólise Epidérmica Tóxica em Medicina Intensiva. *Rev Bras Ter Intensiva*. 2006;18(3):292-297. <https://doi.org/10.1590/S0103-507X2006000300012>
- Estrella-Alonso A, Aramburu JA, González-Ruiz MY, Cachafeiro L, Sánchez MS, Lorente JA. Toxic epidermal necrolysis: a paradigm of critical illness. *Rev Bras Ter Intensiva*. 2017;29(4):499-508. <https://doi.org/10.5935/0103-507X.20170075>
- Neto HC, Chagas BF, Soares MZ, Lachinski RE, Linartevichi VF. Síndrome de Stevens-Johnson associada a fenitoína em pós-operatório de hemorragia intraparenquimatosa cerebral: relato de caso. *FAG Journal of Health*. 2019;1(4):169-184. <https://doi.org/10.35984/fjh.v1i4.110>
- Blum DFC; Silva JAS; Baeder FM, Della Bona A. A atuação da Odontologia em unidades de terapia intensiva no Brasil. *Rev Bras Ter Intensiva*. 2018;30(3):327-332. <https://doi.org/10.5935/0103-507X.20180044>
- Merigo E, Rocca JP, Pinheiro ALB, Fornaini C. Photobiomodulation therapy in oral medicine: a guide for the practitioner with focus on new possible protocols. *Photobiomodul Photomed Laser Surg*. 2019;37(11):669-680. <https://doi.org/10.1089/photob.2019.4624>
- Rocha BA, Filho MRDM, Dos Santos LAN, Silveira SLS, Simões A. Terapia de fotobiomodulação no tratamento das lesões orais da síndrome de Stevens-Johnson: relato de caso. *HU Ver*. 2019;45(4):478-82. <https://doi.org/10.34019/1982-8047.2019.v45.25799>
- Simões A, Freitas PM, Bello-Silva MS, Tunér J, Eduardo CP. Laser phototherapy for stevens-johnson syndrome: a case report. *Photomed Laser Surg*. 2011;29(1):67-69. <https://doi.org/10.1089/pho.2009.2671>
- Pigatto GR, Silva CS, Parizotto NA. Photobiomodulation therapy reduces acute pain and inflammation in mice. *J Photochem Photobiol B*. 2019;196. <https://doi.org/10.1016/j.jphotobiol.2019.111513>
- Paglioni MP, Alves CGB, Fontes EK, Lopes MA, Ribeiro ACP, Brandão TB, et al. Is photobiomodulation therapy effective in reducing pain caused by toxicities related to head and neck cancer treatment? A systematic review. *Support Care Cancer*. 2019;27(11):4043-4054. <https://doi.org/10.1007/s00520-019-04939-2>
- Fiorio FB, Santos SA, Rambo CSM, Dalbosco CG, Serra AJ, Melo BL, et al. Photobiomodulation therapy action in wound repair skin induced in aged rats old: time course of biomarkers inflammatory and repair. *Lasers Med Sci*. 2017;32(8):1769-1782. <https://doi.org/10.1007/s10103-017-2254-2>
- Roviello CF, Rodrigues FSM, Gonçalves JAB, Ferraz RRR. Manifestações e tratamento da necrólise epidérmica tóxica e da síndrome de Stevens Johnson. *J Health NPEP*. 2019;4(1):319-329. <https://doi.org/10.30681/252610103214>
- Reichow SL, Dagnoni C, Maieski A. Necrólise epidérmica tóxica associada ao uso de nivolumabe: um relato de caso. *Braz J Oncol*. 2017;13(46):1-6. <https://doi.org/10.26790/BJO20171346A94>
- Macedo RAP, Morais EF, Dantas AN, Morais MLSA. Chlorhexidine to treat oral mucositis in patients with acute leukemia: systematic review. *Rev Dor*. 2015;16(3):221-226. <https://doi.org/10.5935/1806-0013.20150044>
- Casarolli ACG, Barbosa HB, Paiano LAG, Fernandes LM, Eberhardt TD. Lesões epidérmicas pela síndrome de stevens johnson: cicatrização com uso de membrana de celulose e ácidos graxos. *Estima-Braz J Enterostomal Ther*. 2016;14(3):154-157. <https://doi.org/10.5327/Z1806-3144201600030008>
- Reolon LZ, Rigo L, Conto F, Cé LC. Impacto da laserterapia na qualidade de vida de pacientes oncológicos portadores de mucosite oral. *Rev Odontol UNESP*. 2017;46(1):19-27. <https://doi.org/10.1590/1807-2577.09116>
- Jordal JM, Johnson MI, Iversen V, Aimbire F, Lopes-Martins RAB. Low-level laser therapy in acute pain: a systematic review of possible mechanisms of action and clinical effects in randomized placebo-controlled trials. *Photomed Laser Surg*. 2006;24(2):158-68. <https://doi.org/10.1089/pho.2006.24.158>
- Bohneberger G, Machado MA, Debiasi MM, Dirschnabel AJ, Ramos GO. Fitoterápicos na odontologia, quando podemos utilizá-los? *Braz J Health Rev*. 2019;2(4):3504-3517. <https://doi.org/10.34119/bjhrv2n4-114>

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