

## ORAL GRAFT-VERSUS-HOST DISEASES

Maria Elvira Pizzigatti Correa<sup>1</sup>, Fernanda de Paula Eduardo<sup>2</sup>, Leandro Dorigan de Macedo<sup>3</sup>, Leticia Melo Bezinelli<sup>2</sup>, Paulo Sérgio da Silva Santos<sup>4</sup>, Héilton Spindola Antunes<sup>5</sup>

*1 Oral Medicine Ambulatory, Hematology and Hemotherapy Center, University of Campinas, Campinas, Brazil.*

*2 Hospital Israelita Albert Einstein, São Paulo, Brazil - 3 Dentistry and Stomatology Division, Ophthalmology, Otolaryngology and Head and Neck Surgery Department, Clinical Hospital of Ribeirão Preto School of Medicine, São Paulo University, Ribeirão Preto, SP, Brazil - 4 Department of Stomatology, Bauru Dental School, USP–University of São Paulo, Bauru, SP, Brazil.*

*5 Clinical Research Division, National Cancer Institute of Brazil, Rio de Janeiro, Brazil (INCA).*

### ABSTRACT

The management of graft versus host disease (GVHD) requires a multidisciplinary team, including dentists among others professionals. In 2015 to standardize treatment approaches the Brazilian Society of Bone Marrow Transplantation published recommendation on the management of oral GVHD. Here we update these recommendations including the results of studies published after 2015.

### INTRODUCTION

Graft-versus-host disease (GVHD) is a common complication in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) and is responsible for high morbidity and mortality [26]. GVHD can present in acute and chronic form and usually involves several organs such as: eyes, mouth, skin, liver, intestine and lungs.

The involvement of the mouth in acute GVHD is less frequent than in chronic GVHD, but no less important. Usually in both situations, the oral manifestation of GVHD implies in pain, difficulties on speech, and restriction of food intake, which imply in decrease in quality of life [18, 19]

There are few published papers addressing the manifestation and treatment of oral acute GVHD. In the other hand, for oral chronic GVHD, there are many papers addressing its clinical and histopathological characteristics and management.

This consensus aims to update the previous recommendations of the 2015 Consensus of the Brazilian Society of Blood Marrow Transplantation on the management of oral GVHD, throughout the literature review of papers published after 2015.

### METHOD

A systematic literature review was carried including papers published after 2015 to 2020. A bibliographic

search was carried out using the Pubmed database, including full papers written in English, Spanish or Portuguese. The research was directed to the location of descriptors in titles, abstracts and MeSH of publications with help descriptors (GVHD OR Graft vs Host Disease AND (therapy OR treatment OR treating) AND (Oral Manifestations OR Mouth OR buccal).

### RESULTS

The search resulted in a total of 44 publications, 4 (9%) were excluded after reading the titles. The 40 selected papers were distributed by the six revisors, from which the data used in this study were extracted.

### ACUTE ORAL GRAFT-VERSUS-HOST DISEASE (GVHD)

Although the mouth is not considered a target organ, oral manifestations of acute GVHD can be present in about 0.8% of patients undergoing allogeneic hematopoietic stem cell (HSCT) transplantation who have the acute systemic GVHD.[7, 18, 38]

The diagnosis of acute oral GVHD can be considered as a diagnosis of exclusion. Clinically, it is characterized by the presence of erythema, inflammation, nonspecific ulcerations, atrophy of the oral mucosa and redness of the lips, coinciding with neutrophilic grafting. It is important to point out that, although the oral manifestations of acute GVHD resemble those of oral mucositis, however, oral mucositis is re-

lated to the toxicity of the conditioning regime and it usually presents a resolution prior to or coinciding with neutrophilic grafting [15, 18, 21, 32].

Infections related to the Herpes viridae family are often found in the oral cavity and are related to the degree of immunosuppression induced by the conditioning regime [15, 36, 37]. Clinically herpetic viral lesions in the oral cavity are characterized by ulcerations and pain and may be present even when using antivirals prophylaxis. These injuries are related to increased morbidity [9, 36]. The diagnosis of oral viral infection is usually clinical, but it and can be complemented with a cytological exam (Papa Nicolo), or PCR for Herpes virus.

### TREATMENT

The treatment for oral acute GVHD is mainly topical that can be associated with the systemic treatment protocol for acute GVHD. Mouthwashes with corticosteroids with dexamethasone (0.1mg/mL) and clobetasol (0.5mg/mL) associated or not with tacrolimus (tacrolimus 0.1%)[18, 27] can be use with good response treatment. Patients should be instructed to hold the medication for 5 minutes in the mouth and then, spit out the medication. Food intake, oral hygiene should be avoided for 10-15 minutes after the mouthwash.

The prophylactic use of antifungals is recommended when using mouthwashes with corticosteroids, due to the increased risk of fungal infection. Usually, it is recommended the use of mouthwash with subsequent swallowing of suspension of nystatin [32, 35].

There are one study showing the use of low power laser therapy for treatment of acute GVHD [30] and so far, no recommendation can be done for this treatment modality.

### CHRONIC ORAL GRAFT-VERSUS-HOST DISEASE (GVHD)

The incidence of chronic oral GVHD is approximately 70% to 83% of patients submitted to allogeneic Hematopoietic Stem Cell Transplantation (HSCT).[22, 24] These manifestations may involve the entire oral mucosa, the labial mucosa and even the major and minor salivary glands.

Chronic oral GVHD is clinically characterized by the presence of white lacy lesions similar to oral lichen planus (lichenoid lesions), erythema, inflammation and atrophy of the mucous membranes and also by the presence of oral ulcerations. These changes can be observed in all sites of the oral cavity. Clinically, it can be observed as a single or multiple lichenoid lesion, isolated or associated with redness and ulcer-

ation [14, 32]. In the perioral tissues, chronic GVHD can lead to sclerotic lesions and, consequently, to a decrease in mouth opening. [6, 14, 35]

Chronic GVHD in salivary glands can occur regardless of clinical manifestations in the oral mucosa. [2, 16, 34]. The dryness of the oral cavity can be assessed clinically during the inspection of the oral cavity.[2] Clinical criteria of hyposalivation such as adherence of the wooden spatula to the cheek mucosa, absence of salivary lake in the sublingual region, in addition to the presence of labial dryness can be useful for the diagnosis of dry mouth. Xerostomia can be assessed by the patient's complaint about the needs of fluids to facilitate the ingestion of dry foods.[2, 23]

In addition to the salivary glands, the salivary ducts are also affected by chronic GVHD, which can lead to the formation of pseudocysts of mucous retention (mucocele). Patients can report the formation of small cysts in any region of the mouth, but especially the hard palate, when stimulated by food intake. Ulceration can replace the pseudo cyst when it broken. [32]

In addition to changes in the structures of the salivary glands, and consequently, in the salivary flow, biochemical and proteomic changes in saliva have been reported. [3, 5, 17]

Usually, salivary changes do not respond to systemic treatment of chronic GVHD and it may persist as late effects.[2, 4, 5, 8, 34] Persistent and late changes in saliva are associated with an increased risk of oral infections, especially fungal infections. In addition, they are associated with an increased incidence of dental caries and periodontal disease.[5, 10, 14, 28, 31] Salivary changes associated with changes in the oral microbiota may be associated with the presence of dysgeusia in these patients.[33]

### EVALUATION CRITERIA

The assessment of chronic GVHD activity as well as the criteria for assessing treatment response were published by the National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: NIH Consensus in 2015.[19, 22]

Diagnostic signs and symptoms for chronic oral GVHD include the presence of lichen-like lesions (lichenoid lesions), characterized by the presence of lacy white lines on the oral mucosa. These changes are typically seen in the buccal mucosa and tongue but can be present in the entire oral mucosa and even in the labial vermilion. The lichen-like lesions may or may not be associated with erythema or ul-

cerations, which are not considered as diagnostic features for chronic oral GVHD.[19]

The presence of white plaque without lichenoid characteristics are no longer considered as a clinical diagnostic criteria for chronic oral GVHD. However, these lesions must be considered, evaluated and biopsied, due the high risk of malignant transformation.[19, 25]

Distinctive signs and symptoms for chronic oral GVHD include hyposalivation, presence of mucous retention cyst (mucoceles), oral mucosa atrophy, ulcerations and pseudomembranous ulcerations. In the presence of ulcerations and oral inflammation, fungal, viral or bacterial infections, as well as neoplastic lesions, should be excluded.

Signs and symptoms found in both chronic and acute GVHD are referred as common features and include the presence of inflammation and atrophy in the oral mucosa, erythema and pain.[22]

The objective assessment of the therapeutic response in the oral cavity considers the presence of erythema in the mucosa (color intensity and percentage of the area involved), lichen-like lesions (percentage of the area involved); ulcerations (percentage of the area involved) described on an evaluation scale ranging from 0-12 graduation points. [22]

The subjective evaluation of the therapeutic response includes the presence and intensity of sensitivity to spices, foods, liquids or flavors. This assessment should be made in consideration of the patient's perception during the last week prior to the assessment and is described on a scale of 0-10. For children, the same issues must be addressed, however a sensitivity scale between 0-3 must be used.[22]

Topical treatment of chronic oral GVHD aims to improve symptoms (mainly pain, tenderness and dry mouth), maintain oral functionality and restore mucosal integrity. This can be associated with systemic immunosuppressive treatment, mainly in refractory or difficult to control cases (figure 1). However, special care must be taken when using topical corticosteroids, mainly due to the increased risk of developing oral infections mentioned at the beginning of the chapter.

The performance of oral hygiene during all phases of treatment is extremely important and should be performed after meals and after topical use of corticosteroids. However, due to the variation in the presentation of chronic oral GVHD and the presence of chronic oral pain, oral hygiene must be adapted to the individual conditions of each patient. The use of 0.2% neutral sodium fluoride to prevent tooth decay in the form of mouthwash can be indicated as prophylaxis.[11, 26, 27, 32, 35]

Since the publication of the NIH consensus in 2015, new treatment options for chronic GVHD with oral involvement have been published. These protocols are directed to cases of chronic GVHD refractory to the use of systemic corticosteroids and to calcineurin inhibitors and include Tocilizumab,[21] Ruxolitinib. [1, 20] As topical treatments for chronic oral GVHD associated or not with systemic treatment, the use of platelet rich fibrin gel (PFR) [29] and, low-power laser therapy have been reported with satisfactory results, but with low scientific evidence. [12, 13, 30]

A list of topical management of oral GVHD is shown in figure 1 (Adapted from Carpenter et al, 2015[6] and Wolff et al., 2011[39])

**FIGURE 1-** Supportive therapy for the treatment of oral chronic GVHD

Indication	Preparation	Agent	Concentration	Rating	Comments
Lichenoid lesions / erosions / ulcers	Rinse	Clobetasol Budesonide Dexamethasone Tacrolimus Triamcinolone Prednisolone Clobetasol: Tacrolimus 1: 1	0.5mg / mL (0.05%) 0.3 mg / mL (0.03%) 0.1 mg / mL (0.01%) 1 mg / mL (0.1%) 0.1 mg / mL (0.01%) 3 mg / mL (0.03%) Not specified	Ala BIIa AIII AIII BIIa BIII CIII	Requires nystatin prophylaxis due to the risk of fungal infections
	Gel, paste, ointment	Clobetasol gel Tacrolimus ointment Fluocinonide gel	0.05% 0.1% 0.05%	Ala BIIa BIII	
	Intralesional injection	Triamcinolone	40mg/mL; 0,5mL/cm2	CIIb	

	PUVA/UVB	Psoralen		CII	Refractory disease
Mucosal pain	Rinse	Lidocaine Kaolin-pectin- diphenhydramine- lidocaine 1: 1: 1	2%	BIII BIII	Do not swollen lidocaine – risk for pneumonia
	Not applicable	Low power laser therapy (infrared) for pain relief	Not applicable	CIII	
Xerostomia*	Toothpaste / Liquid Gel	Sodium fluoride	According to the manufacturer	Alb	
	Bubble gum	Salivary stimulants	Per need	AIII	
	Rinse	Water sipping	Per need	AIII	
	Gel or spray	Oral lubricants	Per need	BII	
	Pills	Pilocarpine Cevimeline	5-10 mg X 3-4/d 15-30 mg X 3/d	BIIa BIII	

Adapted from Carpenter, *et al*, 2015[6] and Wolff, *et al.*, 2010[39]

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