

# Brazilian guideline for oral graft-*versus*-host disease: Recommendations from the Brazilian Society of Bone Marrow Transplantation

Leandro Dorigan de Macedo<sup>1\*</sup> , Mariana Andrade Costa<sup>1</sup> , Fernanda de Paula Eduardo<sup>2</sup> ,  
Letícia Mello Bezinelli<sup>2</sup> , Paulo Sérgio da Silva Santos<sup>3</sup> , Héilton Spíndola Antunes<sup>4</sup> ,  
Maria Elvira Pizzigatti Correa<sup>5</sup> 

1. Universidade de São Paulo  – Ribeirão Preto Medical School – Department of Dentistry and Stomatology – Ribeirão Preto (SP), Brazil.
2. Hospital Israelita Albert Einstein  – Faculdade Israelita de Ciências da Saúde – São Paulo (SP), Brazil.
3. Universidade de São Paulo  – Bauru School of Dentistry – Bauru (SP), Brazil.
4. Instituto Nacional de Câncer  – Clinical Research and Technological Development Division – Rio de Janeiro (RJ), Brazil.
5. Universidade Estadual de Campinas  – Hematology and Blood Transfusion Center – Campinas (SP), Brazil.

\*Corresponding author: [dorigan@hcrp.usp.br](mailto:dorigan@hcrp.usp.br)

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## ABSTRACT

Oral chronic graft-versus-host disease (cGVHD) is a frequent and clinically heterogeneous manifestation after allogeneic hematopoietic cell transplantation (HCT). In addition to lichenoid lesions, erythema, and ulceration, the disease can affect the salivary glands, other tissues, quality of life, and is associated with a risk of oral carcinoma. Then, the objective of this study was to update the Brazilian consensus of the Brazilian Society of Bone Marrow Transplantation (Sociedade Brasileira de Transplante de Medula Óssea—SBTMO) on oral cGVHD (2021). A narrative review was conducted including publications from 2021 onward. Evidence and strength of recommendation was graded according to the 2009 Oxford Center for Evidence-Based Medicine. The final recommendations were defined by a panel of SBTMO experts in cGVHD. The most directly applicable evidence supports the use of topical corticosteroids for symptomatic mucosal disease. Photobiomodulation, intraoral ultraviolet B phototherapy, barrier agents, and platelet lysate are promising local options, but supported mainly by small, uncontrolled studies. Ruxolitinib and belumosudil show signals of oral response in patients with refractory disease, but mouth-specific evidence remains observational, secondary or organ-specific, or partially extrapolated; both should be considered conditional second-line or salvage systemic options. Prolonged oral surveillance is necessary due to the risk of secondary oral cancer and other complications. This Brazilian consensus update supports a multidimensional assessment of oral cGVHD and favors local therapy for localized disease whenever feasible. Systemic therapies should be reserved for selected refractory or multiorgan cases, while prevention of oral complications and long-term surveillance remain integral to care.

**Key words:** Graft vs Host Disease. Mouth. Transplantation, Homologous. Saliva. Xerostomia. Therapeutics. Mouth Neoplasms.

## INTRODUCTION

Oral chronic graft-*versus*-host disease (cGVHD) results from a complex interaction between alloreactivity, persistent inflammation, epithelial injury, salivary gland dysfunction, fibrosis, and alterations in local immunity. Clinical manifestations can include lichenoid/reticular lesions, erythema, atrophy, ulceration, superficial

mucocoeles, hyposalivation, xerostomia, sclerosis, and trismus<sup>1–4</sup>. The mouth is a sentinel organ of cGVHD, but also a site where the disease may remain underdiagnosed when symptoms are attributed solely to transplant effects, medications, or infection.

The frequency of oral involvement varies according to the population, diagnostic criteria, time post-transplant, and assessment method. Clinical reviews report oral manifestations in a substantial proportion of patients with cGVHD, with repercussions on pain, eating, hygiene, speech, swallowing, and social life<sup>1,4</sup>. In a Brazilian study, clinical presentation was heterogeneous, reinforcing the need for systematic examination and differentiation between active GVHD, infection, trauma, and potentially malignant lesions<sup>5</sup>.

Saliva should be considered an independent clinical domain. Loss of flow and qualitative alterations in saliva can compromise lubrication, buffering, remineralization, antimicrobial protection, and mucosal integrity. Consequently, xerostomia and hyposalivation can increase the risk of caries, periodontitis, candidiasis, pain, burning, difficulty chewing and swallowing, and altered taste. Recent studies also suggest that oral inflammation and dysbiosis may contribute to the maintenance or exacerbation of cGVHD, although the microbiota cannot be used as a routine clinical biomarker yet<sup>6,7</sup>.

The objective of this consensus was to provide a practical and updated framework for professionals involved in the care of people undergoing allogeneic hematopoietic cell transplantation (allo-HCT), with a focus on oral cGVHD and its complications.

## METHODS

### Search strategy and selection

The search was organized into three dimensions: diagnosis/pathophysiology/epidemiology; treatment; and complications. PubMed, Google Scholar, Scientific Electronic Library Online (SciELO), Web of Science, and ScienceDirect were consulted, combining terms related to cGVHD, hematopoietic cell transplantation (HCT), mouth, oral mucosa, saliva, diagnosis, histopathology, treatment, and complications. References from the previous Brazilian Society of Bone Marrow Transplantation (Sociedade Brasileira de Transplante de Medula Óssea—SBTMO) consensus<sup>8</sup> and the update article published for the international transplant society were also examined.

Publications between 2021 and 2026 were considered eligible. Inclusion criteria required the oral mucosa, oral cavity, salivary glands, or an oral complication to be a primary focus or a defined outcome. Clinical trials, cohort and cross-sectional studies, case series, systematic reviews, consensus statements, and narrative reviews were considered eligible if they contributed to the assessment of diagnostic criteria, safety, epidemiology, treatment, or monitoring. Publications that did not address oral cGVHD, lacked clinically relevant contributions, were not available in sufficient full text for evaluation, or were published in languages not covered by the protocol were excluded.

### Data extraction and critical appraisal

We extracted design, population, definition of oral cGVHD, intervention or exposure, comparator, outcomes, instruments used, quantitative results, follow-up, adverse events, limitations, and applicability. For systemic therapies, overall cGVHD response and mouth-specific response were recorded separately. In studies of complications, we distinguished associations in allo-HCT survivors from evidence directly attributable to oral cGVHD.

### Levels of evidence and grades of recommendation

The 2009 Oxford Center for Evidence-Based Medicine (OCEBM) levels of evidence were used to classify study designs<sup>9</sup>. Recommendations were downgraded when oral specificity was low, a comparator was absent, cointerventions were present, sample sizes were small, outcomes were not validated, or findings were extrapolated from systemic cGVHD. Thus, a high-level systemic study was not automatically interpreted as high-level evidence for the oral mucosa (Table 1).

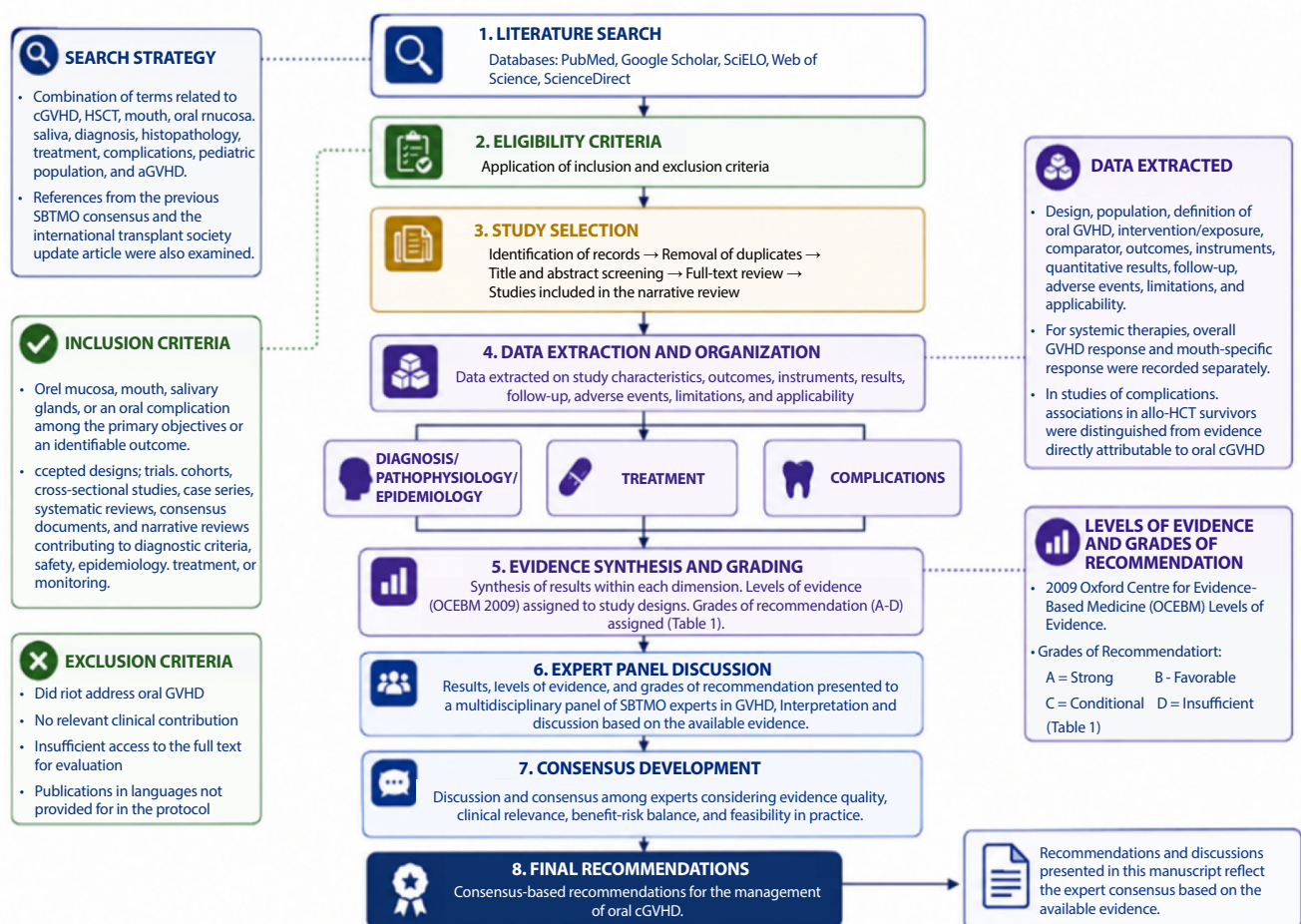
**Table 1.** Grades of recommendation and their interpretation used in this consensus.

| Grade | Interpretation used in the consensus                                                                                                                                                                                                            |
|-------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| A     | Strong recommendation, supported by consistent evidence directly applicable to oral chronic graft-versus-host disease, with likely benefit outweighing risk. No definitive grade A was assigned to interventions in the current <i>corpus</i> . |
| B     | Favorable or reasonable recommendation, with moderate evidence, some heterogeneity, or limited extrapolation.                                                                                                                                   |
| C     | Conditional, adjunctive, or salvage option, supported by small, observational, uncontrolled studies or good-practice consensus.                                                                                                                 |
| D     | Insufficient, indirect, or experimental evidence; use only in the context of research, expert decision, or proposed monitoring.                                                                                                                 |

Source: Adapted from Oxford Centre for Evidence-Based Medicine<sup>9</sup>.

## DISCUSSION AND FINAL RECOMMENDATIONS

Data regarding study designs, results, levels of evidence, and grades of recommendation were presented to and discussed by a multidisciplinary panel of SBTMO experts in cGVHD. The recommendations and discussion presented in this manuscript reflect the expert consensus based on the available evidence. Figure 1 presents the methodological flowchart of the study.



cGVHD: chronic graft-versus-host disease; HSCT: hematopoietic stem cell transplantation; SBTMO: Brazilian Society of Bone Marrow Transplantation (Sociedade Brasileira de Transplante de Medula Óssea); SciELO: Scientific Electronic Library Online; OCEBM: Oxford Center for Evidence-Based Medicine; allo-HCT: allogeneic hematopoietic cell transplantation. Source: Elaborated by the authors with the assistance of generative artificial intelligence (ChatGPT, OpenAI) for visual design and layout.

The scientific content was defined and reviewed by the authors.

**Figure 1.** Methodological flowchart.

## RESULTS

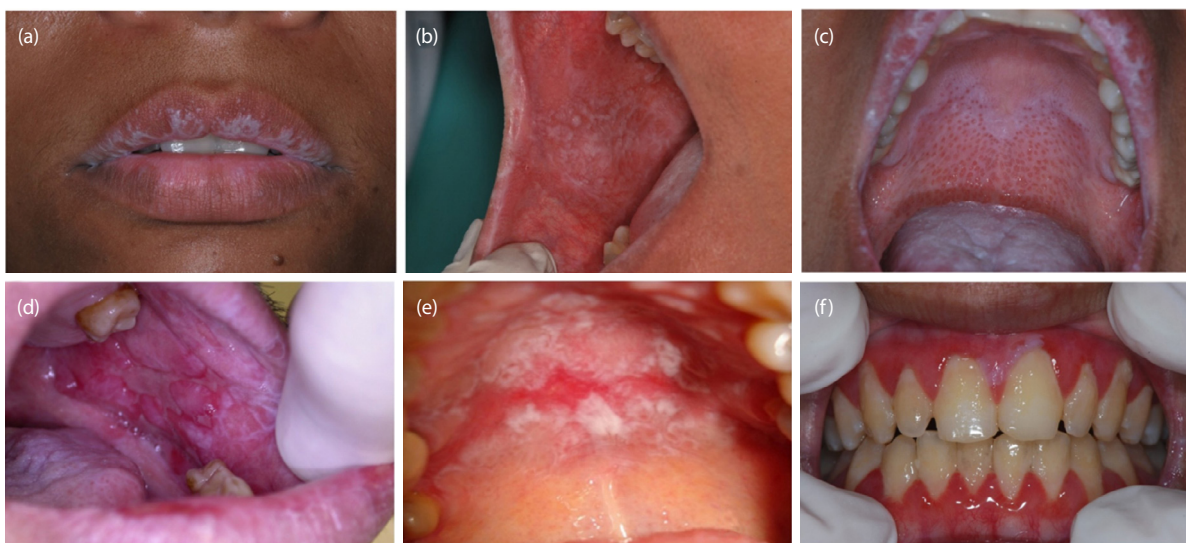
### Clinical manifestations and diagnosis

The epidemiology of oral cGVHD is influenced by age, underlying disease, donor type, prophylaxis, conditioning regimen, time since transplant, National Institutes of Health (NIH) criteria, and assessment method. Variability in denominators and definitions makes it difficult to compare studies and establish a single prevalence.

The most characteristic oral manifestation is the lichenoid or reticular pattern, which may affect the buccal mucosa, tongue, lips, palate, gingiva, and other surfaces. Erythema, atrophy, ulceration, superficial mucocoeles, sensitivity, and dryness may coexist. No single manifestation should be interpreted outside the clinical context; ulcers, erythema, and xerostomia may also result from other diseases, or other treatment related complications<sup>1,5,10</sup>.

The NIH/oral mucosa rating scale (OMRS)<sup>11,12</sup> is useful to track activity and response but should not replace the assessment of symptoms and function. It is important to keep in mind that a low mucosal score does not exclude salivary dysfunction, dietary restrictions, impaired quality of life, or an increased risk of dental caries<sup>13,14</sup>.

Biopsy is not required for every typical presentation, particularly in cases with characteristic lichenoid features, but should be considered when the pattern is atypical, unilateral, persistent, progressive, indurated, exophytic, verrucous, erythroplastic, ulcerated, or unresponsive to adequate treatment. Lesions that change or persist despite cGVHD control should not be automatically classified as cGVHD. Minor salivary gland biopsy may complement mucosal evaluation in atypical or diagnostically uncertain cases; a standardized histopathologic grading system for post-transplant salivary gland changes has recently been proposed<sup>15</sup>. The main differential diagnoses include infections, malignant lesions, and premalignant lesions. Figure 2 presents clinical manifestations of oral cGVHD.



Source: Elaborated by the authors.

**Figure 2.** Clinical manifestations of oral chronic graft-versus-host disease. (a and b) Reticular/lichenoid white striae on the lip and buccal mucosa-diagnostic lesions; (c) multiple mucocoeles on the soft palate and an area with a leukoplakic plaque; (d) ulcerated lesion on the buccal mucosa covered by an adherent pseudomembrane with white reticular/lichenoid striae; (e) leukoplakic plaque with an erythematous area in palate; (f) erythema and edema in gingiva.

### Saliva, microbiota, and pathophysiology

Salivary dysfunction can occur without oral mucosal involvement and may represent glandular damage, medication effects, dehydration, systemic disease, or a combination of these factors. Subjective xerostomia and objective hyposalivation are not equivalent and should be measured separately. Unstimulated and

stimulated salivary flow, standardized collection over a defined time, xerostomia inventory, medication recording, and assessment of mucosal wetness can improve phenotype characterization.

The oral microbiota can influence local and systemic inflammation. Experimental and observational data suggest that dysbiosis may accompany or exacerbate inflammation and cGVHD, but there are no sufficiently validated clinical thresholds, collection methods, or microbiota-based interventions for routine use<sup>6,7,16</sup>. The microbiota should be presented as an axis for translational research.

Histopathological examination of the salivary glands reveals a periductal lymphocytic infiltrate with infiltration and damage to intralobular ducts, fibroplasia in the periductal stroma, and mixed lymphocytic and plasmacytic inflammation with destruction of acinar tissue<sup>10,12</sup>.

## Therapeutic options

### General principles

Treatment should be selected according to the extent of oral disease, symptoms, functional impairment, risk of complications, involvement of other organs, progression, response to prior therapies, infection, cytopenias, and patient preferences<sup>1,10,17</sup>. Exclusively oral and localized disease should, when possible, be treated locally to reduce unnecessary systemic exposure<sup>10,17</sup>. Topical treatment may allow patients to remain off systemic immunosuppression, reduce systemic treatment intensity, or complement systemic therapy<sup>10,17</sup>.

Active, progressive, extensive, disabling multiorgan disease, associated with nutritional compromise or refractory after adequate use of local therapy, requires multidisciplinary discussion. The decision to start systemic immunosuppression should not be based solely on a mucosal score or a single salivary flow value.

### Topical corticosteroids and tacrolimus

The systematic review by Haas and Cruz-Pamplona<sup>17</sup> pooled five oral clinical studies and found signals of benefit for budesonide, clobetasol, and dexamethasone, although with small samples, heterogeneous formulations, short follow-up, and methodological limitations. In a randomized double-blind trial, clobetasol produced greater clinical and symptomatic improvement than dexamethasone<sup>18</sup>. Dexamethasone also showed clinically meaningful first-line activity in a randomized phase II study, whereas the topical tacrolimus arm was terminated early for lack of activity<sup>19</sup>. Budesonide improved oral cGVHD in an open randomized multicenter phase II pilot study<sup>20</sup>. The overall formal classification is baseline 1a; the practical recommendation is grade B, because certainty and applicability are lower than study design alone would suggest.

Dexamethasone, budesonide, and clobetasol can be used as first-line options for symptomatic mucosal disease. Choice should consider extent, potency, contact time, compounding feasibility, adherence, and tolerability. Mouthrinse formulations should be preferred when multiple oral sites are affected, whereas gels, ointments, or Orabase formulations should be reserved for localized lesions and/or lesions refractory to mouthrinse therapy.

Patients should be counseled on technique, contact time, and to avoid eating or drinking immediately after application. The optimal contact time for mouthrinse formulations has been reported to range from 3 to 5 minutes, with a volume of approximately 5 mL. In this context, contact time appears to be more important than the volume used. Prolonged use requires periodic reassessment, inspection for candidiasis, and tapering to the lowest intensity capable of maintaining control. Antifungal prophylaxis should be individualized, not automatic. Table 2 presents the medication options available in Brazil, some of which need to be prepared by compounding pharmacies.

**Table 2.** Corticosteroids and calcineurin inhibitors available in Brazil.

| Class                 | Medication    | Formulation                    | Concentration                     | Remarks                                                                                                                                                                   |
|-----------------------|---------------|--------------------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Corticosteroids       | Clobetasol    | Rinse/gel/paste/cream/ointment | 0.05; 0.01%                       | Rinse should be used when multiple areas of mucosa are affected; gel, ointment, and paste for localized or refractory lesions; injection for refractory ulcerated lesions |
|                       | Dexamethasone | Rinse                          | 0.01%                             |                                                                                                                                                                           |
|                       | Triamcinolone | Rinse                          | 0.01%                             |                                                                                                                                                                           |
|                       |               | Ointment                       | 0.1%                              |                                                                                                                                                                           |
|                       |               | Injection (intralesional)      | 40 mg/mL / 0.5 mL/cm <sup>2</sup> |                                                                                                                                                                           |
|                       | Prednisolone  | Rinse                          | 0.03%                             |                                                                                                                                                                           |
|                       | Budesonide    | Rinse                          | 0.03%                             |                                                                                                                                                                           |
| Calcineurin inhibitor | Tacrolimus    | Gel                            | 0.05%                             | Reserved for corticosteroid-refractory cases; patients may experience intolerance, and systemic absorption can occur                                                      |
|                       |               | Rinse                          | 0.1%                              |                                                                                                                                                                           |
|                       |               | Ointment                       | 0.03%; 0.1%                       |                                                                                                                                                                           |

Source: Elaborated by the authors.

### Photobiomodulation, ultraviolet B, and barrier-protective products

Photobiomodulation with low power laser therapy shows a signal of benefit for pain and ulceration. In small series, there was immediate relief and clinical improvement during induction and maintenance, but recurrence after lengthening the interval between sessions was frequent<sup>21,22</sup>. It should be considered a grade C adjunctive option, especially when the immediate goal is analgesia or when intensification of immunosuppression is to be avoided.

Intraoral narrowband ultraviolet B (nbUVB) phototherapy was described in a series of patients with disease refractory to conventional topical agents. All reported some degree of improvement, but there was recurrence upon discontinuation/reduction, exacerbations, and a lack of uniform comparative criteria<sup>23</sup>. It should be reserved for experienced centers and presented as an emerging grade C therapy.

Barrier-protective gel and autologous platelet lysate showed signals of benefit in uncontrolled studies<sup>24,25</sup>. These therapies can be included as adjuncts or experimental grade C interventions, contingent on infrastructure, consent, and specialized follow-up.

### Systemic therapies for refractory disease

#### Ruxolitinib

Ruxolitinib is a systemic option for cGVHD refractory to corticosteroids and other lines, especially in the presence of multiorgan disease. The oral cohort by Kaurinovic et al.<sup>26</sup> observed a reduction in mucosal score and oral response at four and 12 weeks, with an overall oral response of 81% at 12 weeks, but without a control group, with cointerventions and selection bias. The prospective publication by Bellido et al.<sup>27</sup> reinforced a signal of oral response, but there was a discrepancy between the abstract and detailed analysis; for prudence, the more conservative rate should be used. Long-term systemic follow-up studies suggest that response may be maintained in some patients, but do not substitute for controlled mouth-specific outcomes<sup>28</sup>. The systemic meta-analysis by Fan et al.<sup>29</sup> supports global activity, but application to the mouth remains secondary and heterogeneous.

For oral cGVHD, ruxolitinib should be considered grade C, level 2b in oral studies and 2a with caveats in the aggregate review. Its use requires monitoring for cytopenias, infections, viral reactivation, interactions, and cumulative immunosuppression. It is not first-line treatment for localized oral disease.

## Belumosudil

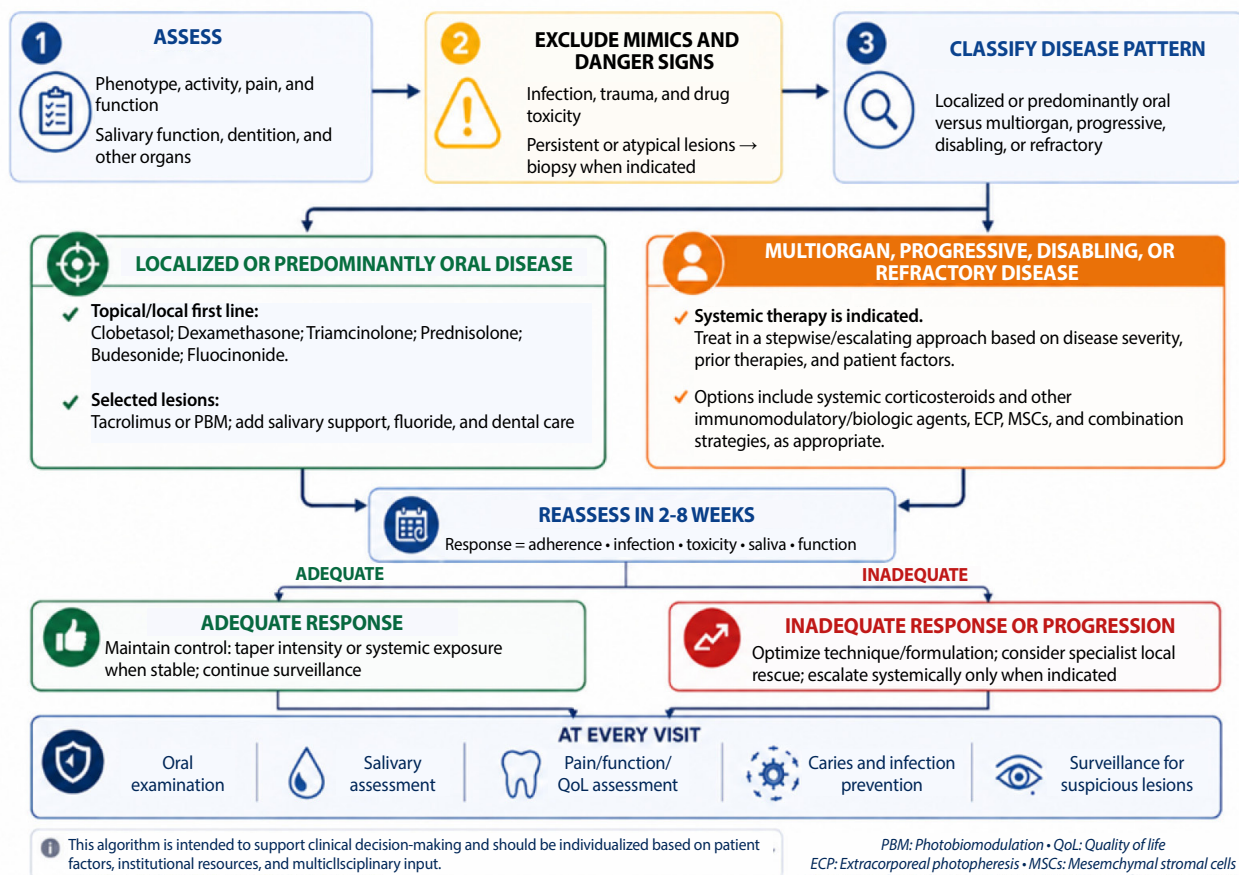
Belumosudil adds a systemic option with antifibrotic and anti-inflammatory plausibility. In the ROCKstar companion study<sup>30</sup>, 20 patients with persistent, multi-refractory oral cGVHD showed a classifiable oral response in 65%, in addition to reductions in collagen, interleukin-17-producing cells, and salivary transforming growth factor (TGF)- $\beta$ 1. French and Italian real-world cohorts also suggest organ-specific activity, but are observational and without mouth-specific controls<sup>31,32</sup>.

Belumosudil may be considered in refractory, fibrosing, or multiorgan oral disease after multiple lines, with grade C and level 2b for oral substudy. Histological and salivary changes should not be presented as proof of restoration of salivary flow or glandular function. Dose, interactions, toxicity, and availability should follow the label and institutional protocol.

## Other therapies

Extracorporeal photopheresis can be used in systemic cGVHD refractory to or dependent on corticosteroids, but the submitted evidence does not present separate oral outcomes<sup>33</sup>. Topical ruxolitinib was studied in skin and should not be recommended for the oral mucosa based on extrapolation from another organ<sup>34,35</sup>.

Figure 3 presents a proposed algorithm for the treatment of oral chronic GVHD. Table 3 provides an overview of the level of evidence and grade of recommendation.



PBM: photobiomodulation; ECP: extracorporeal photopheresis; MSC: mesenchymal stromal cells. Source: Elaborated by the authors with the assistance of generative artificial intelligence (ChatGPT, OpenAI) for visual design and layout. The scientific content was defined and reviewed by the authors.

**Figure 3.** Treatment algorithm for oral chronic graft-versus-host disease.

**Table 3.** Levels of evidence and grades of recommendation for interventions in oral chronic graft-versus-host disease.

| Area                    | Recommendation                                                                                                                      | Level       | Grade |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------|-------------|-------|
| Topical corticosteroid  | Use clobetasol, dexamethasone, triamcinolone, prednisone, budesonide, or fluocinonide as first-line options for symptomatic disease | Baseline 1a | B     |
| Topical tacrolimus      | Consider for localized or refractory lesions                                                                                        | 3b          | C     |
| Photobiomodulation      | Consider as an adjunct for persistent pain and ulceration                                                                           | 4           | C     |
| Intraoral ultraviolet B | Reserve for refractory disease in specialized centers                                                                               | 4           | C     |
| Platelet lysate/barrier | Consider only as adjunctive or experimental                                                                                         | 3b–4        | C     |
| Ruxolitinib             | Consider in refractory oral chronic graft-versus-host disease, mainly multiorgan, with specialized monitoring                       | 2a–2b       | C     |
| Belumosudil             | Consider after multiple lines in refractory/fibrosing or multiorgan disease                                                         | 2b–3b       | C     |
| Xerostomia              | Measure symptoms and flow; combine dental prevention and symptomatic treatment                                                      | 2b–4        | C     |
| Sialagogues             | Individualized trial of pilocarpine/cevimeline when there is glandular reserve                                                      | 4           | C     |
| Caries                  | Fluoride, adapted hygiene, diet control, and dental follow-up                                                                       | 2b–5        | C     |
| Taste/smell             | Actively inquire and assess nutrition when there is functional impact                                                               | 2c          | C     |
| Secondary cancer        | Prolonged oral surveillance and early biopsy of suspicious lesions                                                                  | 2a–2b       | B–C   |
| Salivary monitoring     | Propose a prospective protocol with sialometry, symptoms, oral health, and quality of life                                          | 4–5         | D     |

Source: Adapted from Oxford Centre for Evidence-Based Medicine<sup>9</sup>.

The algorithm should be interpreted as a clinical framework and not as a mandatory sequence. At all levels, infection, trauma, and malignancy must be excluded, and dental care, caries prevention, salivary management, and functional assessment must be maintained.

## COMPLICATIONS

### Saliva and xerostomia

Xerostomia can cause difficulty speaking, chewing, and swallowing, in addition to increasing the risk of caries, candidiasis, and trauma. In a retrospective study of 70 adults, pilocarpine and cevimeline produced modest subjective improvement in dryness score, without demonstration of objective restoration of salivary flow, caries prevention, or comparative benefit<sup>36</sup>. Sialagogues may be individually trialed when there is glandular reserve, with attention to cholinergic effects and contraindications.

A recent narrative review explored the therapeutic potential of photobiomodulation for salivary function recovery across different conditions, highlighting its potential to mitigate inflammatory-phase damage in diseases such as Sjögren's syndrome. However, its efficacy and role in salivary gland dysfunction in cGVHD remain to be established<sup>37</sup>.

### CARIES, DENTITION, AND ORAL HEALTH

Dental health depends on saliva, diet, hygiene, access to dental care, periodontal disease, medications, and the intensity of immunosuppression. In a late cohort of 70 survivors, current oral cGVHD was associated with worse quality of life, greater difficulty with dry foods, and greater dietary limitation, but there was no statistically demonstrated difference in mean tooth loss between groups<sup>38</sup>. Therefore, the consensus should recommend prevention and surveillance, without attributing independent causality to oral GVHD.

Fluoridated dentifrice is recommended, with additional fluoride measures in high-risk individuals, hygiene adapted to pain and sensitivity, reduction of fermentable sugars, hydration, lubrication, and dental follow-up. The clinical practice review reinforces pre-transplant dental assessment—including extraction of non-restorable or infected teeth, periodontal stabilization, and endodontic evaluation, infection prevention, caries control, and specialized referral, although its basis is narrative<sup>39,40</sup>.

For a comprehensive, phase-specific approach to dental management before, during, and after hematopoietic cell transplantation, readers are referred to the companion Brazilian dental consensus series<sup>40–42</sup>.

### **Pain, function, taste, and quality of life**

Pain and sensitivity may impact quality of life more intensely than the extent of mucosal involvement. In a study of 56 patients, pain and sensitivity correlated with Oral Health Impact Profile-14, whereas mucosal severity alone showed no significant correlation<sup>13</sup>. In an objective study of taste and smell, hypogeusia occurred in 68.9% of participants, although some patients did not subjectively recognize the deficit<sup>43</sup>.

Follow-up should include questions about pain, avoided foods, chewing, swallowing, speech, taste, smell, weight, and intake. Patients with nutritional impact should be referred to nutrition and functional rehabilitation. There is insufficient basis to recommend a specific pharmacologic treatment for dysgeusia as standard.

### **Infections, fibrosis, trismus, and osteonecrosis**

Candidiasis and reactivated herpes simplex virus may mimic or worsen oral cGVHD, particularly in the presence of hyposalivation, topical corticosteroid use, or systemic immunosuppression; evaluation should be guided by the clinical phenotype and response to therapy. These risk factors warrant vigilance and targeted treatment when infection is suspected, but do not justify universal prophylaxis<sup>1,44–46</sup>.

Orofacial fibrosis and trismus should be monitored by measuring mouth opening and initiating early stretching exercises when restriction develops. Jaw osteonecrosis should be considered in relation to antiresorptive exposure, corticosteroids, radiotherapy, infection, and other risk factors, rather than attributed directly to oral cGVHD; invasive procedures require individualized hematologic, infectious-disease, and dental/oral-surgery assessment<sup>1,45–48</sup>.

### **Secondary oral cancer and potentially malignant lesions**

Available evidence suggests that oral cGVHD may be associated with an increased risk of secondary oral cancer, although the magnitude and causality of this association remain uncertain because studies are heterogeneous, denominators are inconsistent, and the number of events is often small<sup>49–52</sup>. Persistent cGVHD, prolonged immunosuppression, previous radiotherapy, and host or behavioral factors may modify this risk.

Patients with Fanconi anemia constitute a very-high-risk subgroup because of their inherited DNA-repair defect and predisposition to aggressive head and neck squamous cell carcinoma, including oral cancer; this risk may be further compounded after allo-HCT<sup>53</sup>. Lifelong and more intensive oral surveillance (every six months or less) should therefore be considered mandatory, beginning early after transplantation and coordinated with hematology/transplantation, oral medicine or dentistry, and otorhinolaryngology when indicated. For other allo-HCT recipients, specialized oral examination every 6–12 months is recommended, with shorter intervals and prompt specialist evaluation or biopsy for persistent or clinically discordant lesions<sup>54</sup>.

Table 3 summarizes the levels of evidence and grades of recommendation for treatments related to oral cGVHD.

### Perspectives: early monitoring of salivary function

Salivary gland dysfunction is a clinically significant component of oral cGVHD and can progress even in the presence of stable or minimally symptomatic mucosal disease. Reduced salivary flow can compromise lubrication, swallowing, speech, and mucosal integrity, in addition to increasing the risk of dental caries, opportunistic infections, and a decreased quality of life. However, it has not been established yet whether early detection of glandular hypofunction alters clinical outcomes. We therefore propose an exploratory and longitudinal salivary function assessment that is feasible in clinical practice and can be performed by physicians, nurses, dentists, and other trained members of the transplant team. Unstimulated total saliva could be collected at predefined time points, after 5 minutes of rest, in a pre-weighed container, allowing for the gravimetric calculation of salivary flow in mL/min. The interpretation of sialometry should be integrated with symptoms of xerostomia, clinical examination, dental and periodontal health, the occurrence of oral infections, and the impact on quality of life<sup>55,56</sup>.

Serial evaluation may allow for the identification of trajectories of reduction, stability, or recovery of salivary function and their association with cGVHD activity, oral complications, and patient-reported outcomes. Salivary gland scintigraphy can provide additional functional information but should remain a complementary test, preferably performed at specialized centers or as part of research protocols.

A low flow result alone should not trigger systemic immunosuppression or other disease-modifying treatment; confirmation of the change, repeat measurement, review of reversible factors, preventive oral care, and appropriate referral should precede any therapeutic escalation. This proposal is therefore an SBTMO exploratory perspective, intended to support future trials of early gland-preserving interventions rather than to recommend preemptive treatment.

### CONCLUSION

This Brazilian update recognizes oral cGVHD as a disease affecting mucosa, saliva, and oral function. Topical corticosteroids remain the main strategy for symptomatic, localized oral disease, with potential to reduce systemic exposure. Ruxolitinib and belumosudil can be options for refractory disease, but with conditional recommendations because oral-specific evidence remains limited. Prevention and surveillance for xerostomia, caries, infection, functional impairment, and secondary oral cancer should accompany treatment.

### CONFLICT OF INTEREST

Nothing to declare

### DATA AVAILABILITY STATEMENT

All datasets were generated and analyzed in the current study.

### AUTHORS' CONTRIBUTIONS

**Conception and design:** Macedo LD and Correa MEP; **Acquisition of data:** Macedo LD, Costa MA, Eduardo FP, Bezinelli LM, Santos PSS, Antunes HS and Correa MEP; **Analysis and interpretation of data:** Macedo LD, Costa MA, Eduardo FP, Bezinelli LM, Santos PSS, Antunes HS and Correa MEP; **Manuscript preparation:** Macedo LD, Costa MA, Eduardo FP, Bezinelli LM, Santos PSS, Antunes HS and Correa MEP. **Final approval:** Macedo LD.

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## DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

Chat GPT, Open AI was used as a design-support tool in the development of Figures 1 and 2. The authors reviewed, edited, and take full responsibility for the scientific content and final version of the figure.

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