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Oral Chronic GvHD in Australia: clinical features and challenges in management

Hull K, Ritchie D, McCullough M, Avery S, Kerridge I, Szer J

Correspondence:
Katrusha Hull, Royal Melbourne Hospital, Bone Marrow Transplant Service, Royal Melbourne Hospital, Melbourne, Vic. 3050, Australia.
Email: katrusha.hull@dhsv.org.au

Abstract

Data from the Australasian Bone Marrow Transplant Recipient Registry show a steady increase in the number of allogeneic haemopoietic stem cell transplantations (HSCT) performed annually in Australia and New Zealand. In 2012, 629 allogeneic HSCT were performed. Allogeneic HSCT is associated with numerous potential complications, including chronic graft-versus-host disease (cGVHD). The oral cavity is one of the most frequent sites affected by cGvHD, often leading to significant disability and reduced quality of life. Management strategies are often complex, of variable efficacy and influenced by the availability of various therapeutic agents, access to compounding pharmacies and associated costs. This paper summarises the current status of allogeneic HSCT in Australia and New Zealand with a focus on oral cGvHD and the associated challenges in its management.

Key words:
graft-versus-host disease, oral mucosa, saliva.

Introduction

Allogeneic haemopoietic stem cell transplantation (HSCT), along with the accompanying immunosuppression, is associated with several, potentially debilitating, long-term complications, one of the most significant being chronic Graft-versus-Host Disease (cGvHD). Chronic GvHD is a multisystem immune disorder characterised by immune dysregulation, immunodeficiency, impaired organ function and decreased survival[1]. Nearly 50% of patients who survive longer than 1-year after HSCT develop cGvHD[2]. Factors influencing the risk of

cGVHD onset overall include the use of mobilised peripheral blood stem cells as opposed to bone marrow as the graft source, older donor and patient age and the use of unrelated donors[3]. All of these factors are increasingly common in HSCT practice internationally and will likely result in increased presentations of oral cGVHD. Specific risk factors for the development of oral cGvHD are less well established with the use of peripheral blood stem cells and a prior history of aGvHD identified in the literature[4].

Management of cGvHD remains a significant challenge. One of the most frequent sites affected by cGvHD is the oral cavity which may be the primary or sole site of involvement[5]; Oral cGVHD has a significant and detrimental impact on oral health, function and quality of life.

Therapeutic decisions in the management of oral cGvHD must consider the patient's global disease status and requires close liaison with the patient's transplant physician. Critically, data is scarce on the efficacy of the commonly utilised topical and systemic agents in the management of oral cGvHD with the effectiveness of these agents presumed by extrapolating from their effectiveness in the management of more common, immune mediated mucosal diseases such as oral lichen planus. Management strategies vary between transplant centres and are often based on institutional practice and influenced by the availability of particular agents and formulations, patient acceptance and cost[6].

Allogeneic HSCT in Australia

Allogeneic HSCT has evolved as a curative therapy for haematological malignancy, bone marrow failure, immune deficiencies and some solid tumours. The Australasian Bone Marrow Transplant Recipient Registry has a comprehensive database of transplant activity since 1992. Registry figures demonstrate a steady annual growth in the number of allogeneic HSCT performed in Australia and New Zealand. A total of 570 allogeneic transplants were undertaken in 2013, representing an increase of 16% over a 5-year period[7]. The most common indication for allogeneic transplantation in Australia and New Zealand, as it is internationally, is acute myeloid leukaemia in both the related donor (34%) and unrelated donor (35%) transplant setting[7,8]

Graft-versus-Host Disease is a common transplant-associated complication following allogeneic HSCT, second only to infection. Severe cGvHD is the primary cause for transplant-related mortality (TRM) and is the main contributor to the development of life-threatening opportunistic infection post-HSCT.

The Clinical Spectrum and Diagnosis of Oral cGvHD

The reported incidence of oral cGVHD varies widely with 45-83% of patients who experience cGvHD showing features of oral involvement[6]. Presentations include characteristic lichenoid mucosal lesions, xerostomia secondary to salivary gland involvement or a reduction in oral aperture, resulting from local sclerodermatous disease of the skin.

Mucosal chronic GvHD

In 2005-6 the National Institutes of Health (NIH) proposed simplified and standardised criteria for the diagnosis and staging of cGvHD[9]. The range of clinical signs and symptoms seen in cGvHD was divided by site or organ involved and each feature assigned to either; 1) those deemed to be diagnostic for cGvHD (termed diagnostic features) and 2) those insufficient, when arising alone, to secure a diagnosis of cGvHD due to their non-specific nature (termed distinctive features).

Specific to the oral cavity, the signs and symptoms identified by the NIH consensus papers as diagnostic or distinctive for the presence of oral cGvHD are listed in Table 1[†]. These oral mucosal diagnostic features closely resemble, clinically and histologically, common autoimmune disorders including scleroderma and oral lichen planus (OLP). Any oral site may be affected, however the buccal mucosa, tongue and labial mucosa are most commonly affected[9]. The degree of involvement may be extensive (Figure 1) and lesions can be a source of significant pain, limit nutritional intake and impede overall quality of life[10].

Other conditions, common in the transplant patient may bear a resemblance to the clinical features of oral cGvHD and potentially lead to a mis-diagnosis of cGvHD. Infections including herpetic and fungal, and mucosal trauma are common in the immunocompromised patient, especially those suffering from a dry mouth, and may resemble the white plaques and mucosal ulceration of oral cGvHD (Figure 2). Simple clinical steps are often sufficient to exclude these confounding diagnoses and confirm a diagnosis of oral cGvHD. This may include smoothing of sharp teeth in the vicinity of mucosal trauma and using cotton gauze to identify if a white patch can be removed, as would be seen in candidosis. However occasionally, particularly in the case of persistent oral ulceration, biopsy may be necessary to both confirm the presence of oral cGvHD and exclude malignancy. The histopathological features of oral cGvHD have been previously well described[11].

Salivary hypofunction and xerostomia

Salivary gland dysfunction arising in the acute stages following allogeneic HSCT is predominantly attributable to conditioning regimen toxicity, especially in the case of total body irradiation (TBI), and can persist for many months. Late changes are most often ascribed to cGvHD and clinically resemble the features of Sjögren syndrome[12]. Extensive involvement results in the total destruction of secretory units leading to permanent and profound salivary hypofunction[13]. Salivary gland dysfunction can be the sole manifestation of oral cGvHD and most often presents as the complaint of dry mouth (xerostomia). Critically, the presence of salivary hypofunction is not diagnostic for oral cGvHD[9] due to the existence of several other potential aetiologies, most notably drugs and/or radiotherapy to the head and neck.

Saliva plays a major role in maintaining oral health and oral function. A decrease in the quantity or quality of saliva can have a profound effect on the incidence of dental decay, oral candidosis, the retention of dentures and mucosal friability as well as an adverse impact on speech, swallowing and mastication. Critically, patients report oral dryness as the second most distressing symptom both at discharge and at 1 year after allogeneic HSCT[14]. However, the symptom of xerostomia does not always correlate with clinical signs of salivary hypofunction; likewise clinical evidence of a reduced salivary flow may be demonstrable in patients who do not complain of a dry mouth[15].

Clinical Management of Oral Chronic GvHD

Topical preparations may be the sole therapy for oral cGvHD or may form part of a more complex management schedule. The advantages of topical or local therapies include the application of intensive treatments without necessarily increasing systemic immunosuppression thus maintaining any desirable GVT effects and avoiding systemic toxicities and drug interactions[6]. Critical features of an effective topical or local therapy include substantivity (persistence of therapeutic effect), bioavailability when applied to oral mucosa, acceptable taste and a non-inhibitory cost.

[†] All tables and figures are located at the end of this document.

The management of oral cGvHD can be divided into: 1) management of oral mucosal changes and 2) management of the associated salivary hypofunction. A clinical algorithm for the management of symptomatic oral cGvHD is presented in Figure 4.

Management of the oral mucosal lesions of chronic GvHD

Topical corticosteroids

The mainstay of topical therapy in the management of symptomatic oral cGvHD is steroid preparations formulated in a variety of vehicles, including gels, ointments and rinses, and with varying potency[16]. The most commonly used formulations available in Australia are outlined in Table 2.

Transient burning and the development of secondary oral candidosis are the most common adverse effects of topical corticosteroid therapy. The generalised immunosuppressive and anti-inflammatory effects of topical corticosteroids are believed to play the major role in the pathogenesis of secondary oral candidosis[17]. It has been reported that the presence of oral candidosis may lead to an increase in local symptoms[18] however this is not universally accepted. The development of oral candidosis may delay effective management and obscure the original pathology of interest[19]. Resolution is usually achievable with topical antifungal agents[18], which are generally prescribed in a prophylactic capacity throughout the course of topical steroid therapy. Several topical antifungal agents are available for use; selection of the appropriate vehicle requires consideration of the oral disease status, for example, patients with severely dry or ulcerated tissues do not tolerate the use of a lozenge. An antifungal gel is usually utilised with miconazole gel (Daktarin Oral Gel) the agent of choice however, established drug interactions, especially with warfarin, must be considered (Table 2).

Data demonstrating systemic absorption following application of topical corticosteroids to the oral mucosa is lacking; however caution is required in patients with widespread ulceration due to reduced mucosal barrier function and with prolonged or excessive use[20,21]. Unlike the skin, oral mucosal atrophy is rarely a significant problem with long-term topical corticosteroid use, however for patients with pre-existing mucosal atrophy this may be compounded. For this reason, the use of the least potent agent to achieve therapeutic benefit and discontinuation of treatment when symptoms resolve is recommended.

Alternate topical agents

Effective symptom management with topical corticosteroid therapy is not always achievable prompting the use of topical immunomodulators. A small number of studies have explored the use of topical cyclosporin where oral cGvHD was not responsive to topical corticosteroids. Promising results were shown with cyclosporin in both a mouth rinse and adhesive paste, however, sample size was insufficient to provide a high level of evidence[22,23]. Side effects were reported as mild and usually consisted of transient burning. While the topical cyclosporine mouthwash (Neoral solution) has been utilised in some Australian transplant centres, it is prohibitively expensive and so is not routinely used. In addition, it's unpleasant taste and high (12%) ethanol content makes this solution generally not suitable for the frequently ulcerated and atrophic presentations of oral cGvHD.

Tacrolimus and pimecrolimus are newer calcineurin inhibitors with an improved safety profile in comparison to cyclosporin. In its topical preparation tacrolimus is widely used in the treatment of atopic dermatitis and cutaneous cGvHD. There have been promising results when

used in the management of symptomatic OLP and the oral mucosal lesions of vesiculobullous conditions and Crohns disease, the majority of studies concluding that tacrolimus was at least as effective as topical corticosteroids. This has been recently reviewed elsewhere[24].

Importantly, tacrolimus ointment has shown success in a limited number of studies in patient's with oral cGvHD[25,26]. In clinical practice, there is often a preference for the use of topical tacrolimus where oral cGvHD involves the lips and vermillion as a means for avoiding the potential atrophic effects seen with prolonged topical corticosteroid use in these sites. The use of topical tacrolimus in the management of oral mucosal disease has been shown to have reasonable safety and few adverse effects with those documented including the sensation of mucosal burning, taste disturbance and mucosal staining[24]. Systemic absorption, with therapeutic trough levels, have been reported by some[27] however it is unclear if whole blood tacrolimus levels need to be continuously assessed in patients receiving topical tacrolimus alone, although patients receiving concurrent systemic tacrolimus should be closely monitored.

While tacrolimus ointment generally has an acceptable toxicity profile, the United States Food and Drug Administration (FDA) issued a "black box" warning for tacrolimus due to a theoretical increased risk of malignancy, specifically squamous cell carcinoma (SCC) and lymphoma, when used for cutaneous psoriasis[28]. In Australia, the use of topical tacrolimus is also inhibited by the need for a compounding pharmacist. Ideally tacrolimus is compounded with orabase to form a 0.1% ointment. Paraffin wax has been used for skin preparations, however this is not suitable for oral use due to poor adhesion. For these reasons, tacrolimus use is limited and often restricted to second line therapy when treatment with topical corticosteroids has failed.

Non-pharmacological management strategies form a critical adjunct in the overall management of patients suffering from oral mucosal cGvHD. This includes the avoidance of known irritants such as sodium-lauryl-sulphate (SLS) containing toothpastes and alcohol-containing mouthwashes. A bland diet is recommended and often better tolerated with the avoidance of spices, chilli and acidic foods during symptomatic phases. The use of topical analgesics, such as lignocaine viscous (2% solution, 15ml swished for 30seconds every 3hours) may be helpful when symptomatic oral cGvHD impedes daily activities and nutritional intake.

Management of Xerostomia

Successful management of the symptom of xerostomia associated with cGvHD is often enormously challenging. Temporary relief may be achieved through the use of oral moisturisers, chewing sugar-free gum, saliva substitutes and frequent sips of water. Artificial saliva products are available in various preparations with unique qualities, yet few studies have compared their effectiveness. One study compared the efficacy of commercially available mucin-based products with carboxymethylcellulose (CMC) preparations – finding that mucin-containing products were better tolerated and accepted by patients[29]. Most available products, including those in Australia, are, however, CMC preparations, which increase the viscosity but do not reproduce the physical or chemical properties of saliva[30]. Patient acceptance of these preparations is also often hindered by taste, viscosity, lubrication properties, and poor retention in the mouth[31].

Longer lasting results may be seen with the use of sialagogues, such as pilocarpine hydrochloride, which directly stimulate the salivary glands to increase output. However, functional glandular tissue is required for successful outcomes of therapy. Pilocarpine is most

commonly prescribed for the treatment of glaucoma as a locally acting meiotic agent of the papillary muscles. Via its cholinergic effect, pilocarpine hydrochloride also increases the secretions of exocrine glands including the salivary, lacrimal, sweat and gastric glands along with the mucous cells of the respiratory tract. In Australia off label uses of pilocarpine (Isopto Carpine eye drops) occurs in numerous conditions associated with salivary hypofunction, namely, Sjögren syndrome and more recently salivary hypofunction in cGvHD (Table 3). Adverse effects seen with pilocarpine hydrochloride may include urinary urgency and an increase in perspiration, lacrimation and nausea. More significant adverse effects include an increase in airway resistance and bronchial secretions as well as bradycardia and postural hypotension. Pilocarpine should therefore be avoided in patients with significant comorbidities including pulmonary or gastrointestinal GvHD.

Several studies have shown promising results with pilocarpine therapy for patients who have had head and neck radiotherapy and, more recently, in patients with salivary cGvHD. One study demonstrated a statistically significant difference in salivary flow rate 1hour following administration of pilocarpine hydrochloride (5mg oral pilocarpine, Salagen™)[30]. This same research also found that saliva levels rapidly returned to baseline following cessation of treatment, suggesting that continuous administration is necessary. While longer acting sialagogues have been studied in cGvHD (cevimeline-Evoxac™)[32] of none these are currently available in Australia. Common products used the management of dry mouth are listed in Table 3.

Patients should also be encouraged to use a fluoride containing toothpaste that is also SLS free, as this is often better tolerated. Detailed oral hygiene and dietary instruction is also essential. Saliva is a reservoir for ions that facilitate tooth remineralisation and so avoidance of acidic and sugar-containing foods and beverages are essential in minimising the rampant dental decay that is frequently seen in patients with low salivary flow.

Prognosis and Long-Term Screening

Survivors of allogeneic transplantation face a significant risk of secondary malignancies, with 2-6% of survivors developing a secondary solid malignancy at 10 years[33]. Squamous cell carcinomas of the skin and mouth account for one third of all secondary solid tumours in this group with half of these arising within the oral cavity[34]. Risk factors specific for oral SCC include being male, the underlying disease (specifically Fanconi anaemia), a history of cGvHD and total body irradiation in the conditioning regimen[34,35]. The degree of immunosuppression has also been investigated as a risk factor for secondary solid tumours[35]. While both systemic and topical immunosuppressive therapy have been suggested as potential risk factors for oral SCC exposure to these therapies and the presence of cGvHD are so closely interconnected that it is not possible to attribute specific carcinogenic risk[33].

Examination and surveillance of the oral tissues of survivors of allogeneic HSCT, with timely biopsy of persistent or suspicious lesions to exclude dysplasia or malignancy, should form part of the long-term follow-up and screening following transplantation. Ideally this should be conducted by experienced Oral Medicine specialists in close collaboration with the bone marrow transplant (BMT) team. Guidelines on the long-term management of patients with Fanconi anaemia recommend oral mucosal review on a 6 monthly basis while EBMT guidelines for long-term follow-up of transplant recipients recommend oral mucosal review annually[35,36].

Conclusion

Allogeneic transplantation is increasingly used for a range of diseases in children and in adults. With improvements in transplantation science, HLA-typing and supportive care more patients can anticipate long-term survival following HSCT. Unfortunately, many survivors experience chronic GvHD with oral GvHD a major cause of morbidity and a significant determinant of post-HSCT quality of life. Appropriate management of oral cGvHD is compromised by a paucity of good quality evidence but there are guidelines to optimise oral outcome after BMT and these should be referenced in all BMT service protocols.

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Tables and Figures

Table 1: Classification of the Signs and Symptoms of Chronic GvHD[9]

	Features	Description
Diagnostic Features (sufficient to establish a diagnosis of cGvHD)	Lichen-type features	Fixed, white striations (not removable with cotton gauze)
	Hyperkeratotic plaques	Fixed, white plaques (not removable with cotton gauze)
	Restriction of mouth opening from sclerosis	Fibrosis/hardening of the peri-oral tissues on palpation and reduction of oral aperture
Distinctive Features (insufficient alone to establish a diagnosis)	Xerostomia*	The subjective complaint of oral dryness
	Mucocoeles	A usually painless, smooth surfaced mass. May appear clear or bluish in colour and be numerous (Figure 3)
	Mucosal atrophy*	
	Pseudomembranes*	
	Ulceration*	
Common Features (seen in both acute and chronic GvHD)	Gingivitis	
	Mucositis	
	Erythema	
	Pain	

* In all cases, infection, drug effects, malignancy, or other causes must be excluded

Table 2: Topical corticosteroids plus common anti-fungals used in the management oral cGvHD

Potency	Generic Name	Concentration	Brand	Instructions for use
Mild (Class I)				
	Hydrocortisone acetate	1.0% ointment	Sigmacort	Apply thin film 2-4 times daily after meals
Moderate(Class II)				
	Triamcinolone acetonide	0.02% ointment 0.1% emollient	Aristocort Kenalog in Orobase	Apply thin film 2-3 times daily after meals
	Betamethasone valerate	0.02%, 0.05% ointment	Betnovate	Apply thin layer 2-3 times daily after meals
	Fluticasone propionate	125cg/dose inhaler	Flixotide Metered Dose	1-2 sprays directed at lesion, 2-4 times daily (max 8 spray doses per day)
Potent (Class III)				
	Betamethasone valerate	0.1% ointment	Betnovate	Apply thin film 2-3 times daily after meals
	Betamethasone diproprionate	0.05% ointment	Diprosone	Apply thin film 2-3 times daily after meals
	Dexamethasone 4mg tablet	0.25mg/ml solution (0.5mg/rinse)	1 tablet dissolved in 160ml water	Gently swish with 20ml for 5min then spit out. Repeat 3-4 times daily
	Prednisolone 5mg tablet	0.5% solution	Dissolve 1 tablet in 10ml water	Gently swish with entire solution for 5min then spit out. Repeat 3-4 times daily. Bitter taste may affect compliance- dexamethasone solution preferred.
	Mometasonefuroate	0.1% ointment	Elocon	Apply thin film 1-2 times daily

Super potent (Class IV)			
Betamethasone dipropionate	0.05% OV*	Diprosone OV	Apply thin film 1-2 times daily
Intra-lesional injection			
Triamcinolone acetonide	10mg/ml	Kenocort-A 10	Maximum 1mg/injection site, repeat at ≥ 1 week intervals if required
Commonly used topical antifungals			
Miconazole	20mg/g	Daktarin Oral Gel	Place ½ of provided scoop on tongue, hold for as long as possible then swallow. Alternatively, patients using an ointment TC can mix both 1:1 Be aware of drug interactions, especially Warfarin
Nystatin	100 000 U/ml (dropper bottle)	Nilstat Oral Drops	Swirl 1ml in mouth for as long as possible then swallow. Repeat QID Alternatively, patients using mouthwash TC can add 1 drop to each mouthrinse. Contains sucrose-not for prolonged use in dentate patients

* OV- optimised vehicle, TC- topical corticosteroids,

Table 3: Management of xerostomia in chronic GvHD

Use	Specific agent	Main ingredients	Instructions for use
SLS free toothpastes (fluoride containing)	Biotène Toothpaste	0.14% w/v sodium monofluorophosphate	
	Oral Seven toothpaste	0.76% w/w sodium monofluorophosphate	
	Curasept chlorhexidine toothpaste	0.05% fluoride 0.05% chlorhexidine	
	Curaprox Enzycal	sodium fluoride 950ppm	
	Xerostom toothpaste	Sodium fluoride 995ppm	Online only
Sialagogues	4% Isopto Carpin Eye Drops (15ml)	pilocarpine hydrochloride	Place 3-4 drops on a spoon, stir into a small amount of water. Drink solution immediately. Repeat 3 times daily
Mucosal lubricants	Biotène Oralbalance gel	Glycerin and sorbitol base 1. Carbomer 2. Hydroxyethycellulose 3. Sodium hydroxide	Apply on fingertip to affected areas when required, especially at night. Biotène® range: mouthwash, spray
	Oral Seven Gel	Glycerin, sorbitol base 1. Aloe barbadensis 2. Lactoperoxidase 3. Glucose 4. Lactoferrin, Lysozyme	Apply by fingertip to affected areas when required, especially at night. Oral Seven range: mouthwash, spray
	Hamilton Aquae Oral Gel	Carmellose sodium 20mg/g	PBS approval for 4months in palliative care where dry mouth is a symptom
	Hamilton Aquae Liquid	Per ml contains: Sorbitol solution 42.86mg Carmellose sodium10mg	1-2 sprays into mouth as required. PBS approval for 4months in palliative care
	Xerostom® Gel (biocosmetic laboratories)	Glycerin based Extra virgin olive oil Provitamin B_5 Provitamin E Parsley oil (See fact sheet for full list)	Apply by fingertip to affected areas when required, especially at night. Online only. Xerostom range: spray, pastilles, gum, mouthwash
	General salad oils	Patients can use any palatable salad oil as an oral lubricant e.g. coconut oil, olive oil etc	Place a small amount in mouth, use tongue to spread over affected tissues

Figure 1: Extensive ulceration of oral chronic GvHD

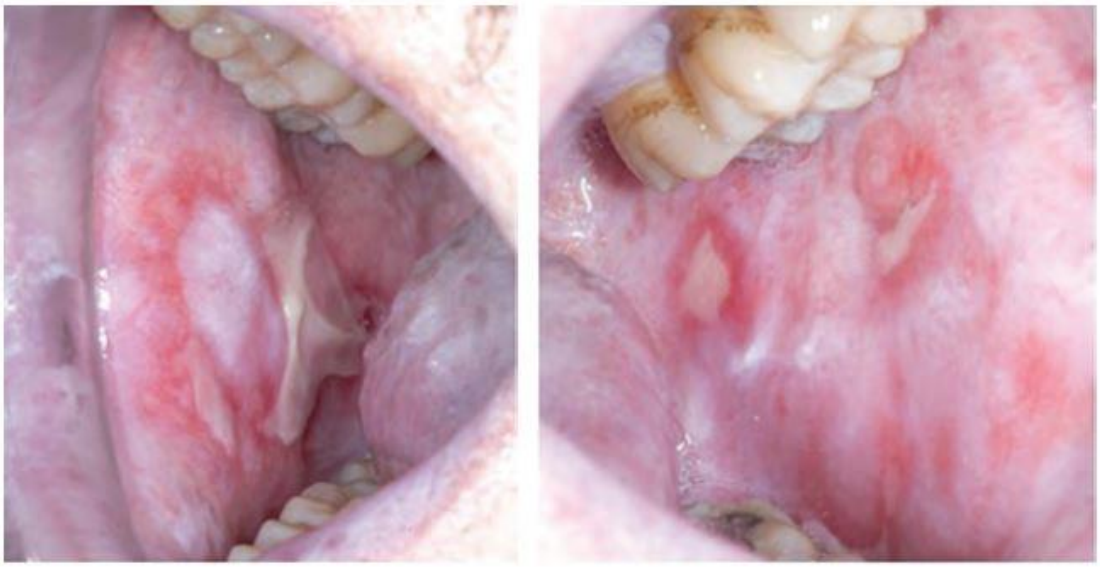


Figure 2: Patient 6 months post allogeneic HSCT with intra-oral HSV ulceration

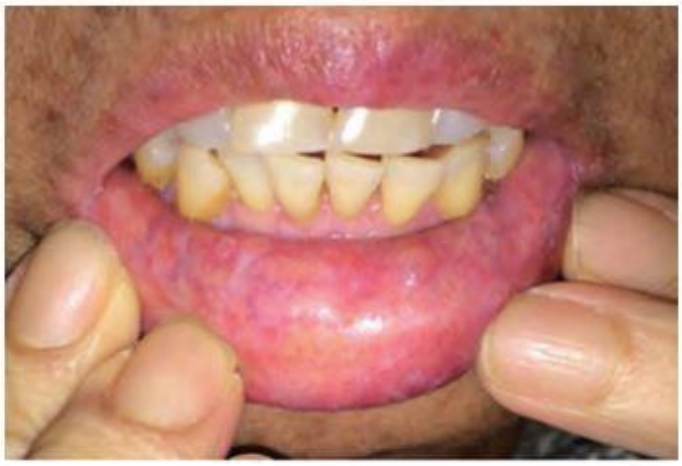


Figure 3: Mucocoeles on the lower labial mucosa of a patient with oral cGvHD

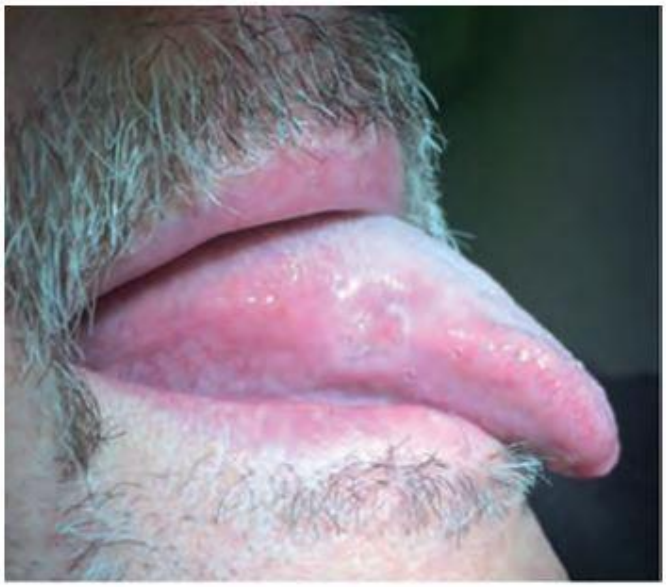
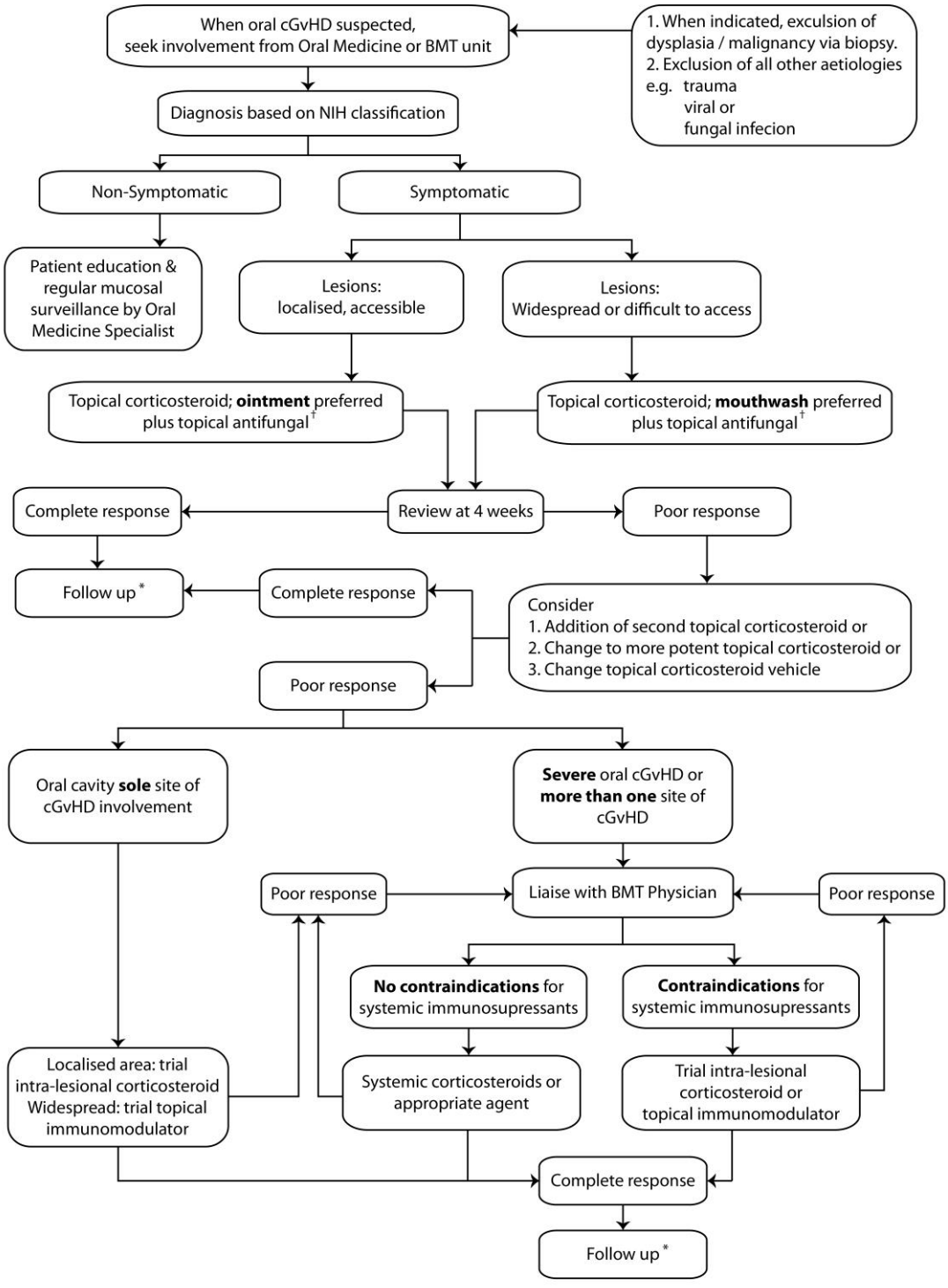


Figure 4: Clinical algorithm for symptomatic management of mucosal oral cGvHD



† The appropriate topical anti-fungal agent should be selected for each patient with reference to GvHD presentation and potential drug interactions.
* Follow up: patient should be reviewed at 4 weeks to confirm maintenance of symptom control. Biannual mucosal surveillance recommended.