

Graft-versus-Host Disease: Mouth

Celebrating a Second Chance at Life Survivorship Symposium

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Chronic Graft-versus-Host Disease and Your Mouth

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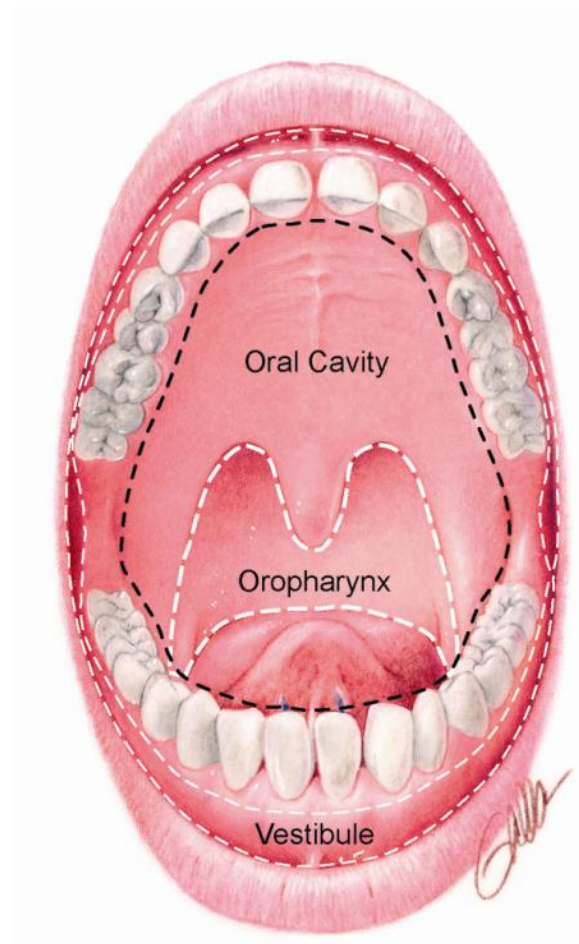
Mass General Brigham

No disclosures relevant to this presentation

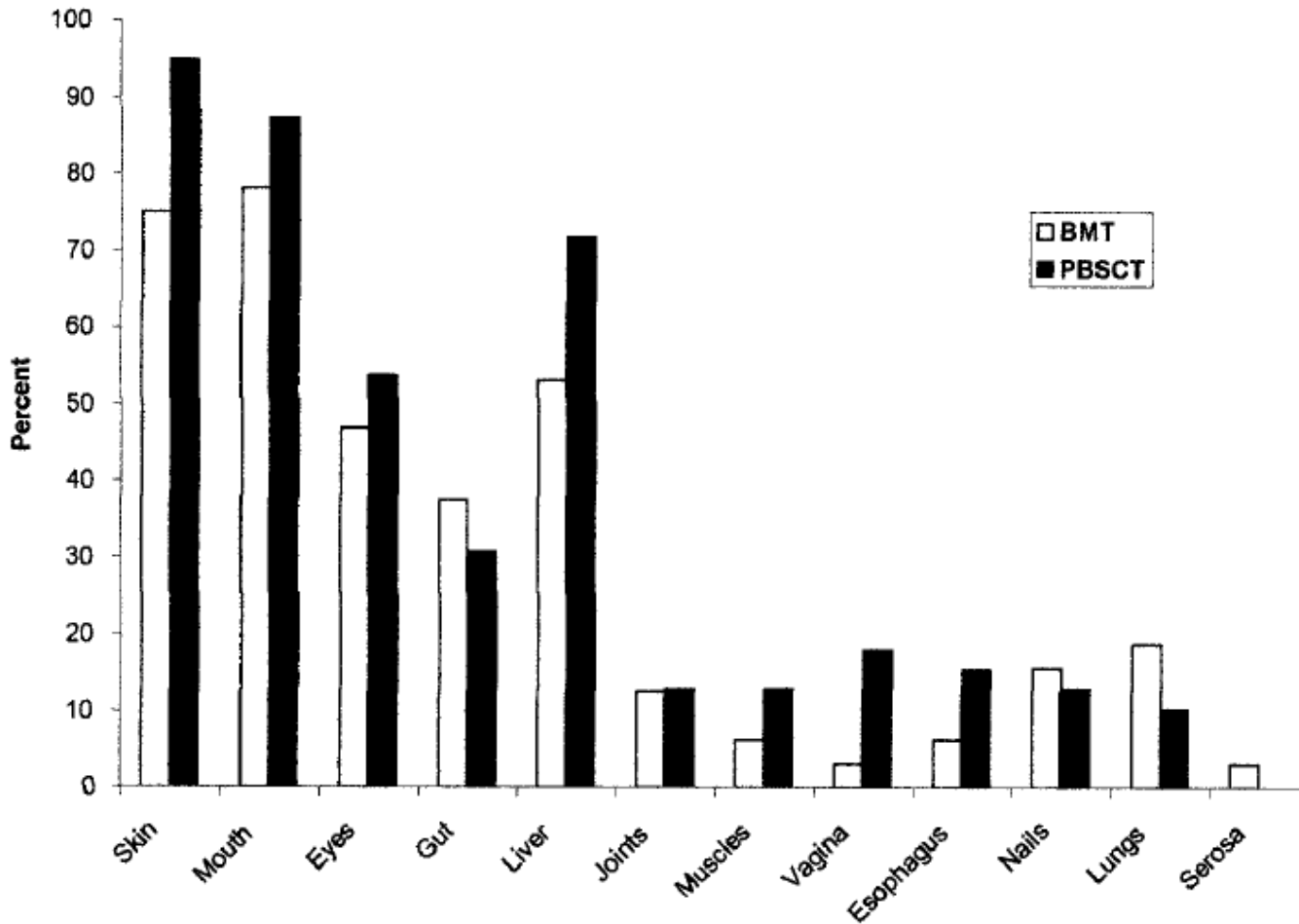
Includes off-label use of FDA approved medications

Oral chronic graft-versus-host disease

- Mouth involvement is common, often prominent
- Range of severity, symptoms
- Lichenoid inflammation and mouth sensitivity
- Lip chapping, blisters
- Dry mouth, cavities, infections
- Oral cancer risk



Oral cGVHD is very common



- Infections
- Pulmonary decline (SOB, dyspnea, hypoxemia)
- Endocrinopathies
- Metabolic abnormalities
- Arthralgias/myalgias/fasciitis/contractures
- Oral/dental complications
- Nutritional compromise
- Side effects of chronic immunosuppression (second malignancies, bone density, end-organ toxicity)
- Functional disability- physical, emotional, role, social, sexual
- Distressing symptoms including fatigue, odynophagia, dysphagia, pruritis, ocular pain and dryness
- Body image changes
- Psychosocial distress and adjustment difficulties characteristic of chronic illness

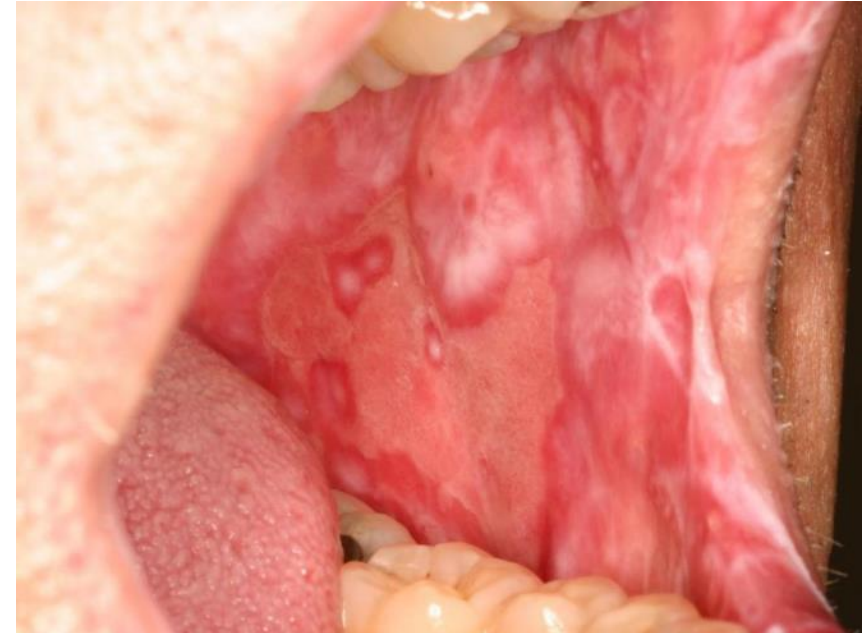
“While oral lesions are most common in patients with extensive chronic GVHD, patients in our and other centers have been described who have limited disease involving only the oral cavity.

In addition, we have noted that the oral cavity can be the site of persistent activity after the resolution of chronic GVHD affecting other sites.”

Schubert M, Sullivan K. Recognition, Incidence, and Management of Oral Graft-Versus-Host Disease. NCI Monographs 1990;9:135-43

Oral cGVHD features

- Resembles immune/autoimmune conditions
 - lichen planus
 - Sjögren syndrome
 - scleroderma
- Impacts oral health/quality of life
- May not respond to systemic therapy, or limited to mouth
 - *important role for ancillary care*



Treister N, et al. Blood 2012;120:3407-3418



Oral mucosal cGVHD



Salivary gland cGVHD



Sclerotic cGVHD

Oral mucosal cGVHD		Salivary gland cGVHD		Sclerotic cGVHD	
Signs	Symptoms	Signs	Symptoms	Signs	Symptoms
<ul style="list-style-type: none"> ● Lichen-type features* ● Hyperkeratotic plaques* ● Erythema/atrophy† ● Ulcerations with pseudomembranes† ● Atrophic glossitis ● Superficial mucocele† 	<ul style="list-style-type: none"> ● Sensitivity to foods/drinks <ul style="list-style-type: none"> - Spicy/seasoned foods - Acidic foods (citrus, salad dressing, carbonated drinks) - Alcoholic beverages and alcohol containing mouth rinses - Salty foods - Hard/crunchy/crusty foods - Warm (temperature) foods/drinks ● Sensitivity to mint-flavored toothpaste/brushing ● Taste changes 	<ul style="list-style-type: none"> ● Thickened, sticky, ropery or foamy saliva ● Lack of saliva/absence of floor of mouth pooling ● Atrophic mucosa ● Dental caries (interproximal and at the cervical margins) ● Oropharyngeal candidiasis ● Frequent water sipping ● Tongue “clicking” while speaking ● Food debris inside the mouth ● Inability to eat dry foods without fluids 	<ul style="list-style-type: none"> ● Xerostomia† ● Sensitivity to foods/drinks ● Difficulty speaking ● Difficulty chewing ● Difficulty swallowing/throat constriction ● Waking at night because of severe dryness ● Taste changes 	<ul style="list-style-type: none"> ● Restriction of mouth opening from sclerosis* ● Leathery skin ● Mucosal bands 	<ul style="list-style-type: none"> ● Difficulty eating ● Jaw pain ● Tightness

*Consensus criteria diagnostic features.

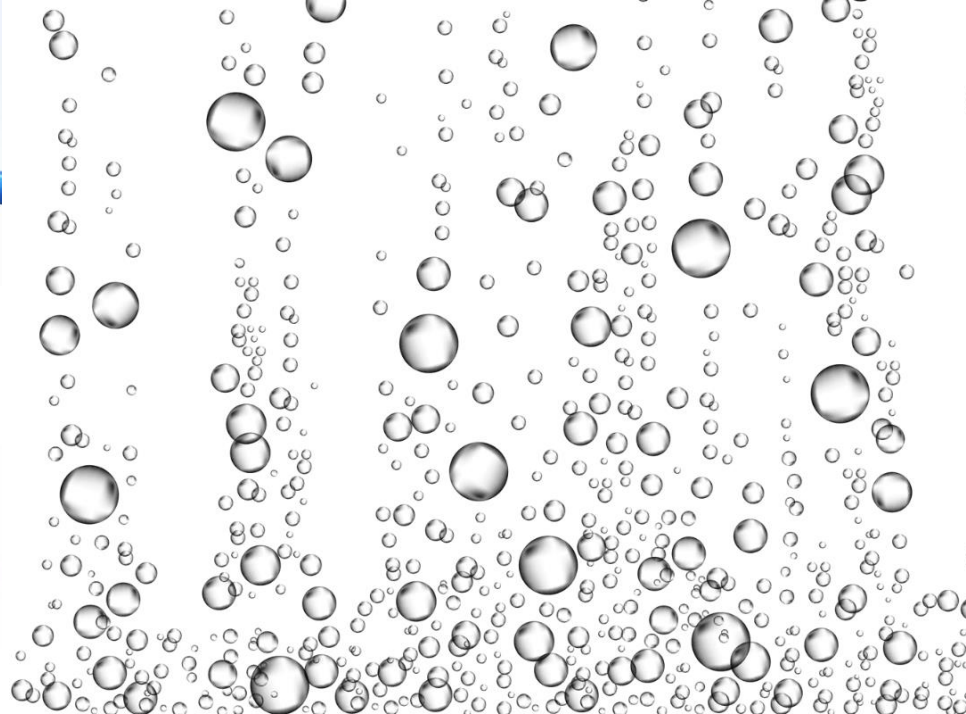
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Oral mucosal cGVHD

- “Lichenoid” pattern of inflammation
 - white striations, redness, ulcerations
 - cheeks and tongue common
 - Lips dry, sensitive, inflammation
- Discomfort and sensitivity
 - eating/drinking
 - acidic, spicy, hard/crunchy
 - brushing teeth
- Limited mouth opening, tightness

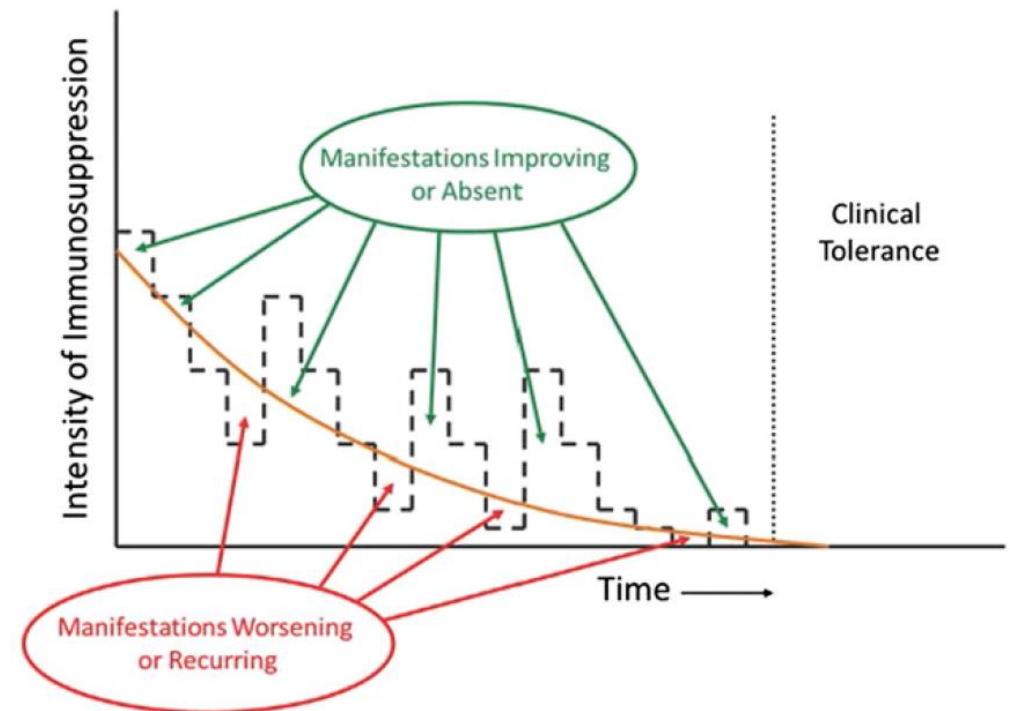






Management of mucosal cGVHD

- Topical corticosteroids
 - general considerations
 - gels (2-4x/day, gauze)
 - clobetasol 0.05%
 - fluocinonide 0.05%
 - solutions (5 min, 2-4x/day)
 - dexamethasone 0.5 mg/5mL
 - *clobetasol 0.05%*
 - *budesonide 0.03%*
- Topical tacrolimus
 - Protopic 0.1% ointment (lips)
 - *tacrolimus 0.5 mg/5mL*
- Combination therapy
- Intralesional steroid therapy
- (children's toothpaste 😊)



Flowers M, Martin P. *Blood* 2015;125:606-615; Carpenter P, et al. *Biol Blood Marrow Transplant* 2015;21:1167-87



Oral infections common in cGVHD

- Oral candidiasis (thrush)
 - contributing factors
 - immunosuppression
 - dry mouth
 - topical steroids
 - dentures
 - antifungal therapy
 - topical/systemic
 - long-term prophylaxis
- Herpes simplex virus (HSV) recrudescence
 - immunosuppression
 - “breakthrough” infections
 - antiviral therapy







Salivary gland cGVHD

- Functions of saliva
 - lubrication/chewing
 - taste
 - antimicrobial
 - buffering/remineralization
- Quantitative/Qualitative changes
 - xerostomia/discomfort
 - difficulty eating/swallowing
 - dental cavities
 - gumline, in between teeth
 - recurrent yeast infections

TABLE 1
The Major Functions of Saliva

Functions	Salivary Components Involved
(1) Protective functions	
Lubrication	Mucins, proline-rich glycoproteins, water
Antimicrobial	Amylase, complement, defensins, lysozyme, lactoferrin, lactoperoxidase, mucins, cystatins, histatins, proline-rich glycoproteins, secretory IgA, secretory leukocyte protease inhibitor, statherin, thrombospondin
Growth factors	Epidermal growth factor (EGF), transforming growth factor-alpha (TGF- α), transforming growth factor-beta (TGF- β), fibroblast growth factor (FGF), insulin-like growth factor (IGF-I & IGF-II), nerve growth factor (NGF)
Mucosal integrity	Mucins, electrolytes, water
Lavage/cleansing	Water
Buffering	Bicarbonate, phosphate ions, proteins
Remineralization	Calcium, phosphate, statherin, anionic proline-rich proteins
(2) Food- and speech-related functions	
Food preparation	Water, mucins
Digestion	Amylases, lipase, ribonuclease, proteases, water, mucins
Taste	Water, gustin
Speech	Water, mucins



Management of salivary cGVHD

- Saliva substitutes, stimulants, sialogogue therapy (pilocarpine)
- Prevention of cavities
 - brushing/flossing/diet
 - fluoride
 - prescription gel
 - varnish
 - remineralizing agents
- Routine dental visits
 - bitewing radiographs
 - caries control
- Antifungal therapy for recurrent yeast infections



Figure 15. Intraoral bitewing radiograph demonstrating multiple interproximal dental caries (radiolucencies) in a patient with salivary gland chronic GVHD.

Oral sclerotic cGVHD

- Reduced mouth opening
 - tightening of skin
 - fibrotic cheek “bands”
 - functional impact
- Mucosal defects
 - focal gum recession
 - loss of vestibules
- Pain, multifactorial
- Management challenging



Oral squamous cell carcinoma risk

- Oral cancer can present with variable features
 - non-healing/worsening sore
 - ulcer, mass, induration
 - may appear similar to GVHD
- Importance of routine follow-up; biopsy suspicious lesions
- Patient awareness

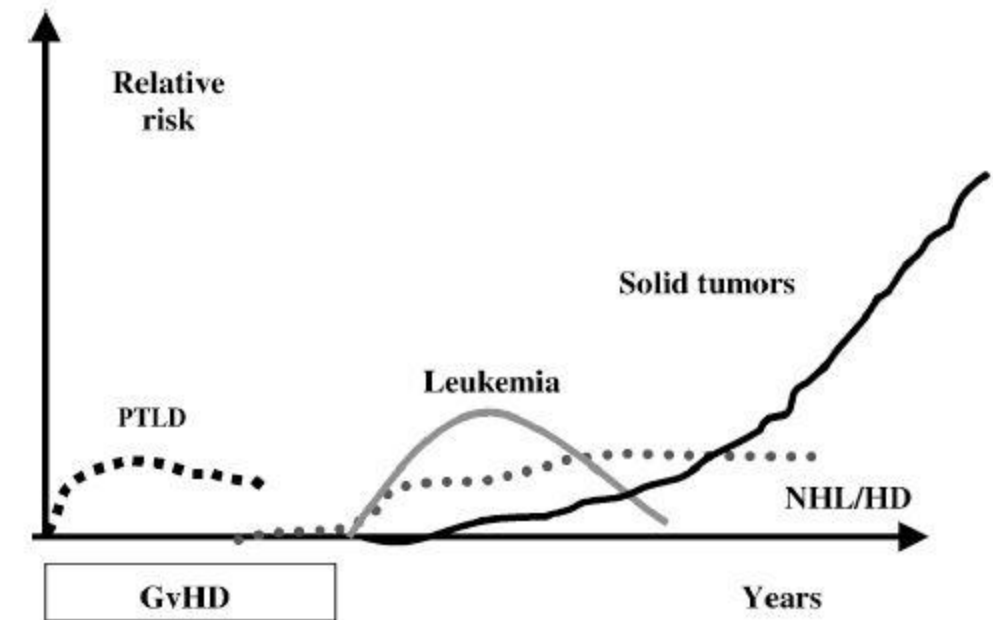
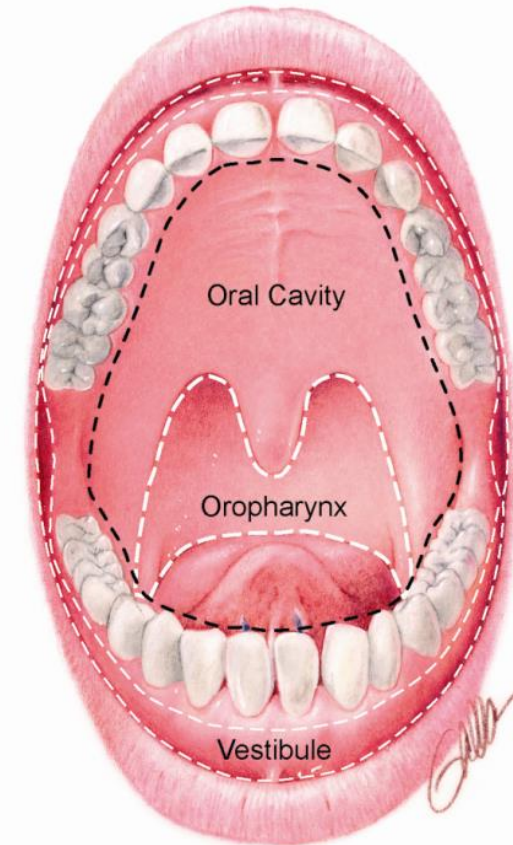


Fig. 1 Scheme of time course and relative risk of second malignancies after allogeneic stem cell transplantation.



Oral cGVHD summary

- Common, may be first site of cGVHD, may persist for months/years
- Oral sensitivity and dry mouth most common symptoms
- Management
 - avoid irritating food/drink/toothpaste
 - topical corticosteroids & tacrolimus
 - salivary stimulants & moisturizing agents, Rx sialogogues, fluoride
- Routine dental care, dental radiographs, preventive care
- Oral cancer risk awareness and screening



Common Prescriptions – Oral Mucosal cGVHD

Solutions/Rinses

- Best for generalized/extensive involvement
- 3-5 minutes, 2-4x/day
- Dexamethasone 0.5 mg/5 mL solution
- Compounded prescriptions
 - budesonide, clobetasol, tacrolimus

Gels, Creams and Ointments

- Good for limited involvement
- Dry affected area, can apply with gauze, leave for 5-10 minutes, 2-4x/day
- Fluocinonide 0.05% gel
- Clobetasol 0.05% gel
- Protopic 0.1% ointment (Lips)

Common Prescriptions – Salivary Gland cGVHD

- Stimulants and Moisturizing Agents
 - Biotene™ mouthwash/gel
 - Sugar-free candy/gum
- Prescription sialogogues
 - Pilocarpine 5 mg 3x/day
 - Cevimeline 30 mg 3x/day
- Fluoride (caries prevention)
 - Prevident 5000 (nightly)
 - Varnish (office application)
- Remineralization
 - GC MI Paste Plus™

Table 4. Guidelines for screening, prevention, and management of late complications in patients with oral cGVHD

Late complication	Prevention	Screening	Management
Oral squamous cell carcinoma	Smoking cessation Moderate alcohol consumption	Annual clinical examination Biopsy of atypical/suspicious lesions	Referral to multidisciplinary head and neck oncology center
Rampant dental caries	Minimize intake of refined carbohydrates (especially sugar-containing soft drinks) Brush at least twice daily, after eating when possible Floss daily Fluoride 1.1% gel paint on or in custom trays, daily Remineralizing agent, apply with fluoride Professional fluoride varnish application	Increased risk in patients with significant salivary gland cGVHD Increased risk in patients with orofacial sclerotic cGVHD Increased risk in patients with severe mucosal disease and avoidance of oral hygiene Examine teeth for evidence of cervical demineralization/decay Twice annual dental visits <ul style="list-style-type: none"> ● Soft and hard tissue examination ● Bitewing radiographs (annual) 	Treat dental caries as soon as diagnosed Careful follow-up for new or recurrent caries Reinforce oral hygiene and dietary habits Reinforce daily preventive measures
Fibrosis	No known preventive measures	Ask patient if aware of tightness/limited opening Extensive sclerotic skin disease, especially with neck involved Examine for intraoral buccal fibrotic bands by palpation	Physical therapy Intralesional steroid therapy Surgery Systemic therapy for systemic involvement

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Free GVHD Resources

Graft-versus-Host Disease: What to Know, What to Do

(BMTInfoNet.org/GVHD-Patient-Handbook)

- Developed with GVHD experts
- Covers GVHD for all organ sites; info on therapies and side effects

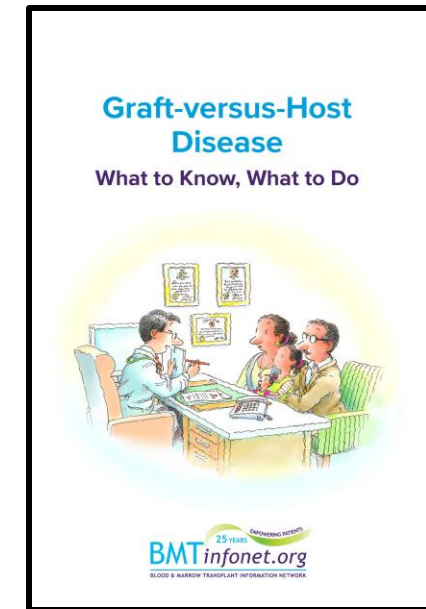
BMT InfoNet online information (BMTInfoNet.org/GVHD)

NMDP fact sheets (bit.ly/3T481V8):

- Eyes, lungs, mouth, skin, connective tissues, GI tract, genitals
- Developed with experts from the Chronic GVHD Consortium

NMDP free transplant guidelines mobile app

- Includes chronic GVHD symptom checker tool
- Search “transplant guidelines” in app stores





Questions?



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