Oral complications in hematopoietic stem cell transplantation

Center For Oral Disease
At Brigham and Women's Hospital

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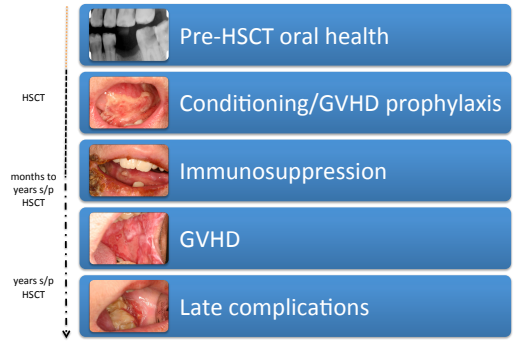
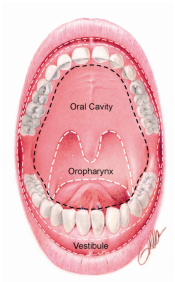
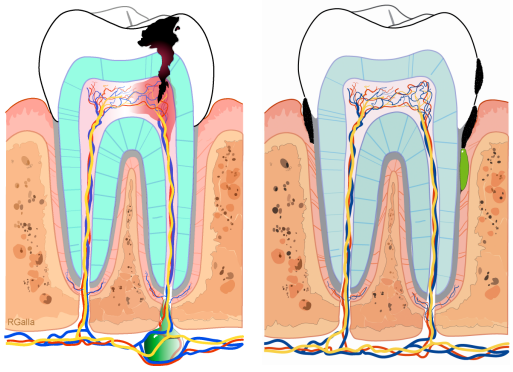


Why the oral cavity?

- "High traffic" site
- Dental and periodontal disease common
- HSV trigeminal latency
- GVHD common, significant impact
- High risk site for secondary cancer





Pulpal abscess Periodontal abscess

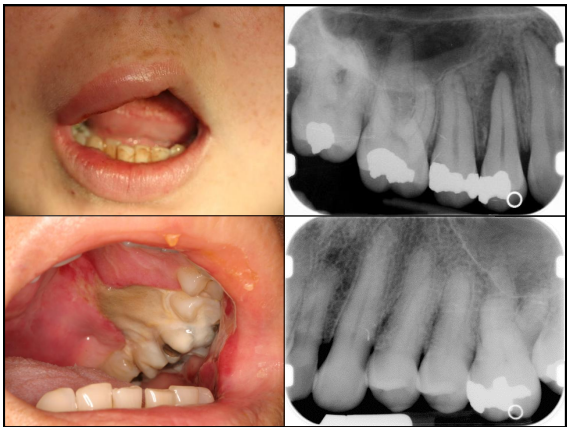
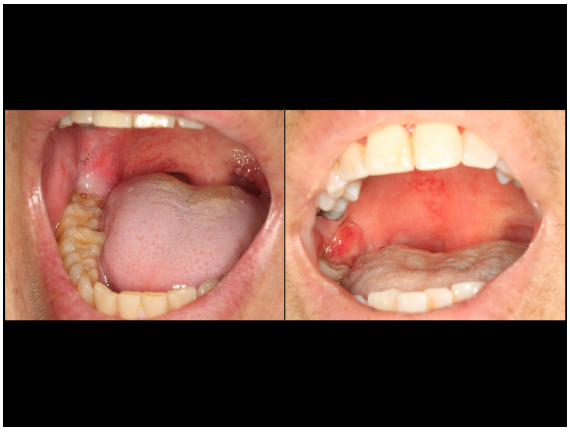
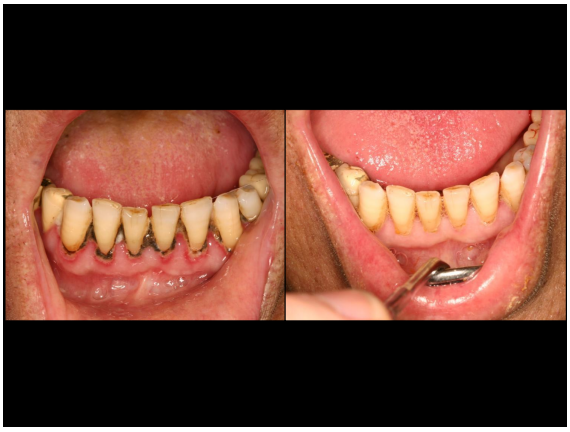


Table 28-1. Pre-HSCT Dental Evaluation Guidelines

Finding/Complication	Evaluation/Test	Treatment
Soft tissue infection	Examination, culture, biopsy	Definitive antimicrobial therapy, prophylactic therapy throughout HSCT
Dental caries	Clinical examination, full mouth series of dental radiographs, vitality testing	Treat caries, begin endodontic therapy or extraction of abscessed and nonvital teeth, and teeth with untreated periapical radiolucencies
Periodontal disease	Periodontal examination, radiographs	Scaling and root planing, extraction of hopeless teeth
Pericoronitis	History of recurrent pain/swelling associated with third molars, examination, radiographs	Extraction of associated third molar >2 weeks before hospital admission

In: Wingard JR, et al. eds. *Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians* Bethesda, MD: AABB, 2009





ACYCLOVIR PROPHYLAXIS OF HERPES-SIMPLEX-VIRUS INFECTIONS

A Randomized, Double-Blind, Controlled Trial in Bone-Marrow-Transplant Recipients

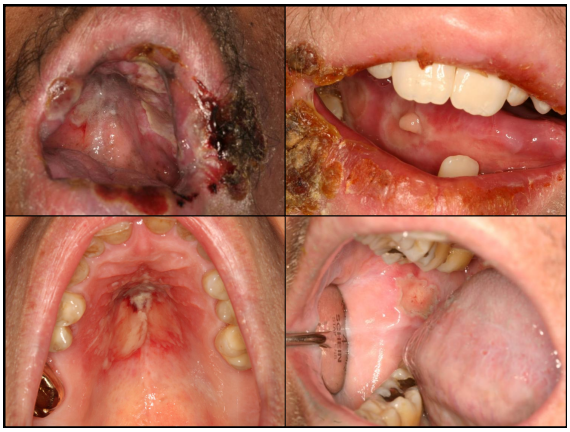
REIN SARAL, M.D., WILLIAM H. BURNS, M.D., OSCAR L. LASKIN, M.D., GEORGE W. SANTOS, M.D., AND PAUL S. LIETMAN, M.D., PH.D.

Abstract We conducted a double-blind, placebo-controlled study of acyclovir prophylaxis against infection with herpes simplex virus (HSV) in 20 seropositive recipients of bone-marrow transplants. Acyclovir or placebo was administered for 18 days, starting three days before transplantation.

Culture-positive HSV lesions developed during the study in seven of the 10 patients who received placebo. In contrast, no such lesions appeared in the 10 patients who received acyclovir ($P \simeq 0.003$). None of the patients had evidence of drug toxicity.

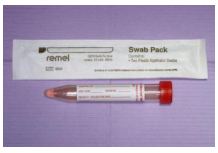
Five of the patients treated with acyclovir had mild culture-positive HSV infections after cessation of the drug, and two additional patients shed virus without having lesions.

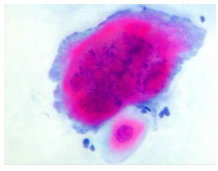
Acyclovir appears to be a potent inhibitor of HSV replication. Although acyclovir does not appear to eradicate latent infection, it can provide effective prophylaxis against reactivated infections. (N Engl J Med. 1981; 305:63-7.)



Recrudescent HSV infection

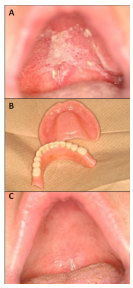
- Atypical presentations
- Breakthrough possible
- Diagnosis
  - culture/cytology
  - biopsy rarely
- Management
  - increase ACV dose
  - valacyclovir
  - foscarnet, cidofovir

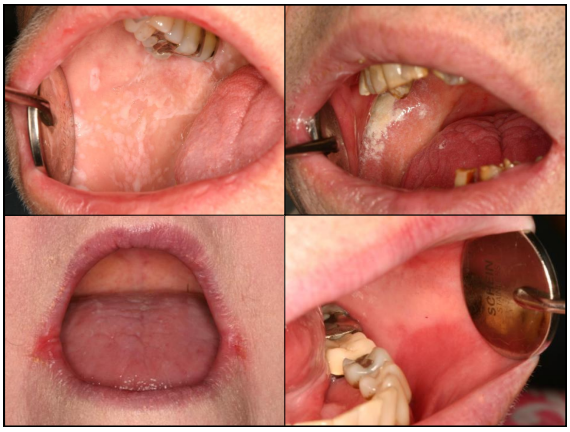




Candidiasis

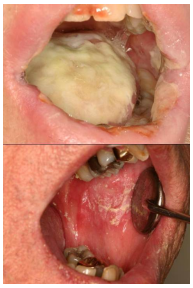
- Risk factors
- Clinical forms
  - pseudomembranous
  - atrophic/erythematous
  - angular cheilitis
- Clinical diagnosis
- Management
  - topical
  - systemic
  - long-term strategies





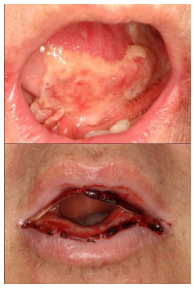
Fungal testing

- Culture
  - culture if systemic therapy ineffective
  - speciation & susceptibility testing
- Cytology
  - to confirm diagnosis
  - unable to perform susceptibility testing



Oral mucositis

- Primary risk factors
  - conditioning regimen
  - GVHD prophylaxis
- Clusters w/ other toxicities
- Clinical impact
  - pain, dysfunction
  - associated outcomes



Sirolimus for GVHD prophylaxis

- Treatment groups
  - rap/tac (n=30)
  - mtx/tac (n=24)
- Severe mucositis
  - 7% vs. 50%
- Duration of opioids
  - 13.5d v s.17d
- Length of stay
  - 18d vs. 22d

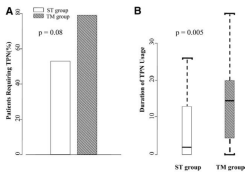


Figure 3. TPN use and duration of use. A, Less TPN was used in the ST group ($P = .08$). B, The duration of TPN use was significantly shorter in the ST group ($P = .005$).

Cutler C, et al. BBMT 2005;11:383-8

NCCN mucositis guidelines

General considerations

- Patient education and communication
- Routine assessments w/ valid scale
- Good oral hygiene = GCP
- Bland oral rinses throughout (e.g. saline)

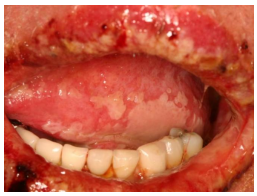
Interventions

- Bland rinses, devices
- Topical anesthetics
  - viscous lidocaine
  - "magic mouthwash"
- Systemic analgesics
- Diet modifications
  - soft, bland foods
  - avoid acidic, spicy

Bensinger W, et al. JNCCN 2008;6 suppl1,s1-20

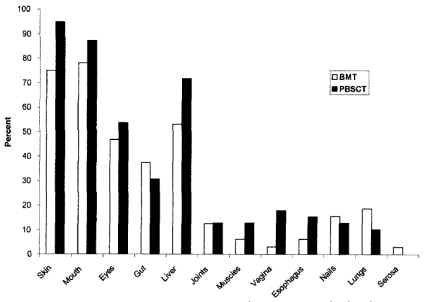
Oral acute GVHD?

- Mouth <u>infrequent</u>
  - after mucositis "window"
  - must r/o HSV
- Concurrent skin, liver, gut involvement
- Clinical features
  - non-specific ulcerations
  - lips frequently affected
- Ancillary management w/ topical steroids



Ion D, et al. Characterization of oral involvement in acute graft-versus-host disease. Oral abstract. American Academy of Oral Medicine 2011, Puerto Rico

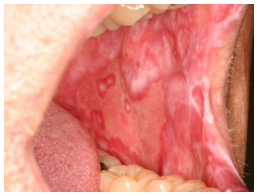
Oral chronic GVHD is very common



Flowers M, et al. Blood 2002;100:415-419

Oral cGVHD features

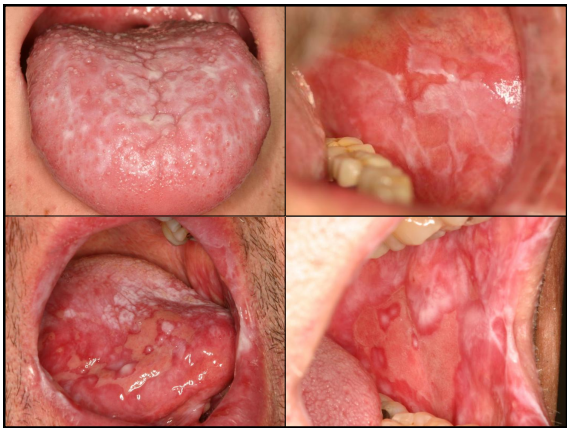
- Resembles immune/ autoimmune conditions
  - lichen planus
  - Sjögren syndrome
  - scleroderma
- Frequently refractory to systemic therapy
  - *important role for ancillary care*

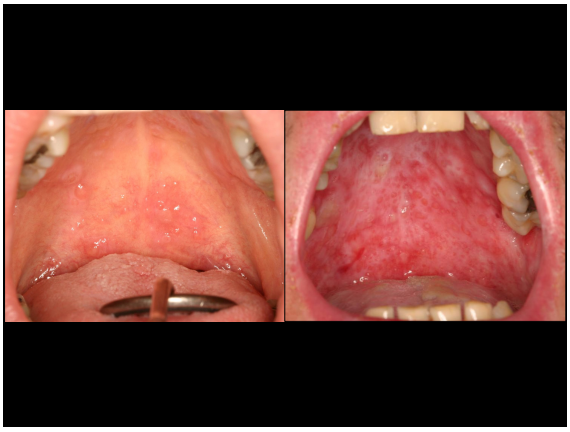


Oral mucosal cGVHD		Salivary gland cGVHD		Sclerotic cGVHD	
Signs	**Symptoms**	**Signs**	**Symptoms**	**Signs**	**Symptoms**
• Lichen-type features* • Hyperkeratotic plaques* • Erythema/atrophy† • Ulcerations with pseudomembranes† • Atrophic glossitis • Superficial mucoceles†	• Sensitivity to foods/drinks - 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	• Thickened, sticky, ropey 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	• Xerostomia† • Sensitivity to foods/drinks • Difficulty speaking • Difficulty chewing • Difficulty swallowing/throat constriction • Waking at night because of severe dryness • Taste changes	• Restriction of mouth opening from sclerosis* • Leathery skin • Mucosal bands	• Difficulty eating • Jaw pain • Tightness

*Consensus criteria diagnostic features.
†Distinctive (supportive but nondiagnostic) features.

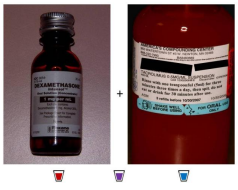
Treister N, et al. Blood 2012;120:3407-3418

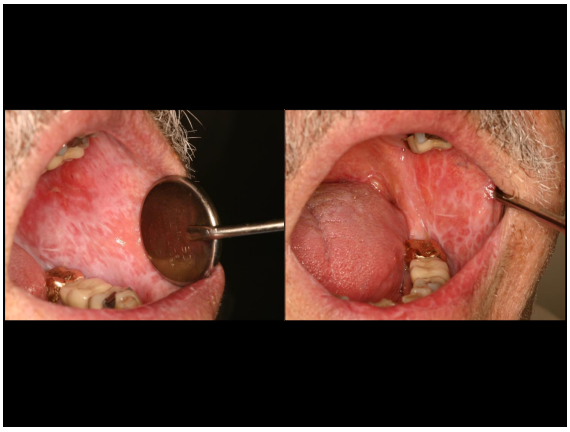


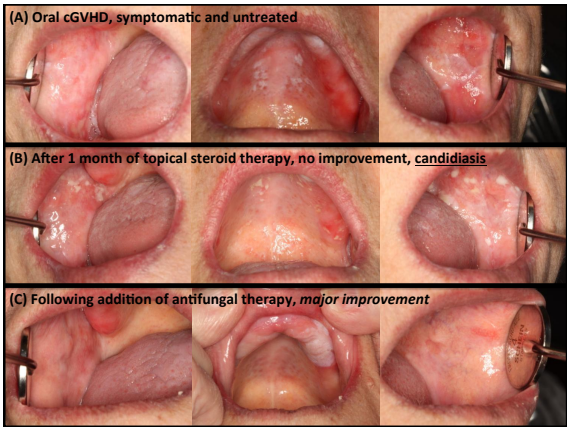


Management of mucosal cGVHD

- High potency topical corticosteroids
  - clobetasol 0.05% gel
  - fluocinonide 0.05% gel
  - dexamethasone 0.5 mg/5 mL (5 min swish/spit)
  - clobetasol 0.05% solution (compound)
- Topical tacrolimus
  - Protopic 0.1% ointment (lips)
  - tacrolimus 0.5 mg/5 mL (compound)
- Combination therapy







Salivary gland cGVHD

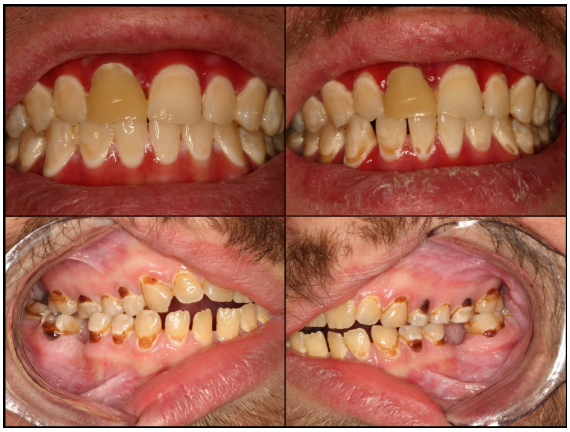
- Functions of saliva
  - lubrication/mastication
  - antimicrobial
  - buffering/remineralization
- Quantitative/Qualitative changes
  - xerostomia/pain/discomfort
  - difficulty eating/swallowing
  - dental caries
    - cervical, interproximal
  - recurrent candidiasis

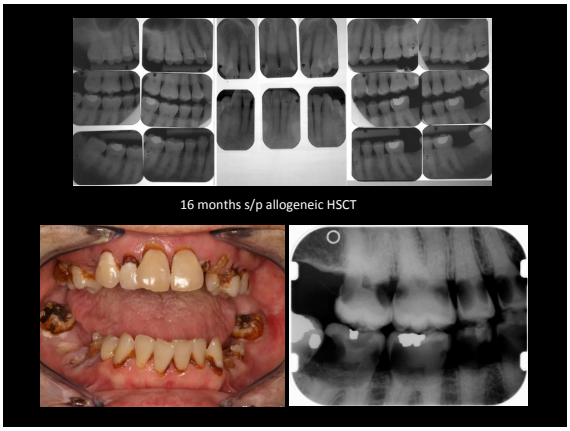
TABLE 1
The Major Functions of Saliva

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), nerve-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

Adapted from FDI Working Group 10, Core (1992), and Fox (1989).

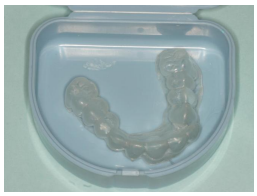
Kaufman E, et al. Crit Rev Oral Biol Med 2002;13:197-212





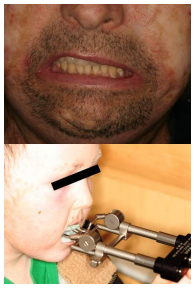
Management of salivary gland cGVHD

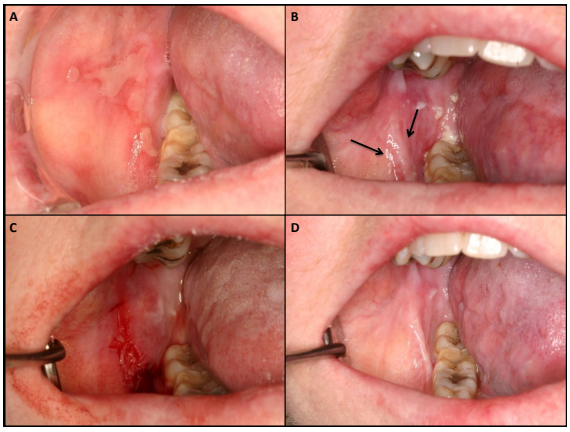
- Caries prevention
  - brushing/flossing/diet
  - fluoride
    - trays w/ 1.1%/0.4% gel
    - varnish
  - remineralizing agents
    - (eg GC MI Paste Plus)
- Routine dental visits
  - radiographs/caries control
- Saliva substitutes, stimulants, sialogogues
- Diet modifications



Sclerotic cGVHD

- Tissues affected
  - facial and perioral skin
  - buccal mucosa "bands"
  - *poorly described in literature*
- Clinical impact
  - trismus
  - pain, dysfunction
  - periodontal complications
  - impaired hygiene





Squamous cell carcinoma

- Major risk factors
  - cGVHD
  - duration of IST
  - males>females
  - younger age at HSCT
- Risk increases w/ time post HSCT
  - overall risk 4.6-8.3x >10 y
- Oral cavity
  - buccal cavity/pharynx
  - 7.01-11.1x overall
  - 25.7-77.9x >10 y

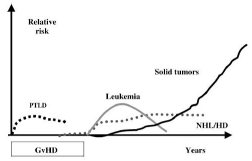
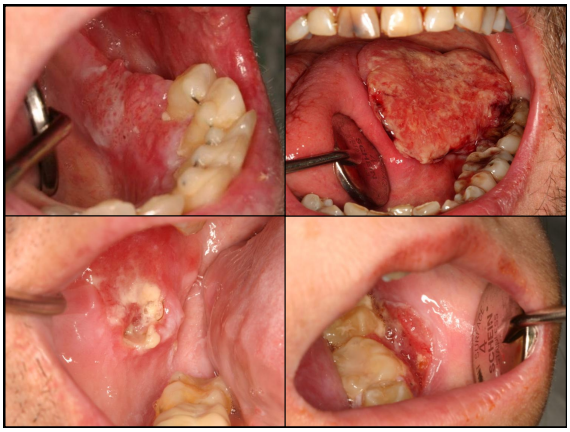
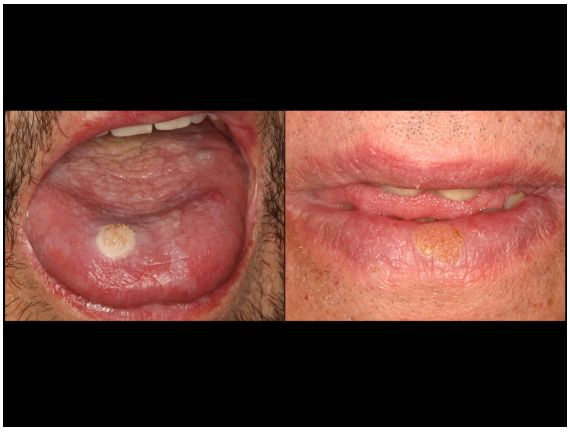


Fig. 1 **Scheme of time course and relative risk of second malignancies after allogeneic stem cell transplantation.**

Curtis R, et al. New Engl J Med 1997;336:897-904
Curtis R, et al. Blood 2005;105:3802-11
Ades L, et al. Blood Reviews 2002;16:135-46
Rizzo J, et al. Blood 2009;113:1175-83





Summary

- Oral complications in HSCT are common
- Education, prevention, anticipation
- Management requires correct diagnosis
- Oral medicine integral part of HSCT team

Chapter 28

Oral Complications in Hematopoietic Stem Cell Transplantation

Nathaniel S. Treister, DMD, DMSc, and Stephen T. Sonis, DMD, DMSc

I. INTRODUCTION

In: Wingard JR, et al. eds. *Hematopoietic Stem Cell Transplantation: A Handbook for Clinicians* Bethesda, MD: AABB, 2009

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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 were severe mucosal disease and avoidance of oral hygiene Examine teeth for evidence of cervical demineralization/decay Twice annual dental visits ● 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

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