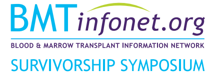

Your Mouth and Chronic Graft-versus-Host Disease

Celebrating a Second Chance at Life
Survivorship Symposium

April 30 - May 6, 2022

Nadarajah Vigneswaran BDS, DMD, FAAOMP,DABOMP
UTHealth School of Dentistry at Houston

Your Mouth and Chronic Graft-versus-Host Disease

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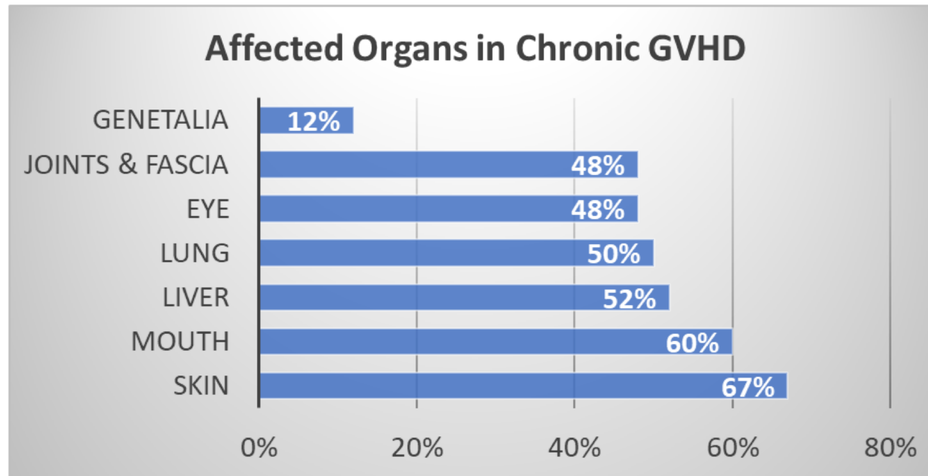
Mouth involvement in Chronic GVHD is common



Prevalence of Oral cGVHD:

- 45% -83% in patients with cGVHD
- Adults >>> Children

Jacobsohn, D.A., et al., Correlation between NIH composite skin score, patient-reported skin score, and outcome: results from the Chronic GVHD Consortium. Blood, 2012. 120(13): p. 2545-52; quiz 2774.

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Oral chronic GVHD can affect the entire mouth

- Can cause
  - Mouth sores
  - Throat sores
  - Chapped lips
  - Dry mouth
  - Tooth decay
  - Infection
  - Increased risk of oral cancer

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Oral problems caused by chronic GVHD

- **Opportunistic fungal (candidiasis) and viral (HSV and HZV) infection**
  - Chronic oral sores due to yeast or herpes infection
- **Oral lichen planus-like lichenoid changes**
  - Chronic inflammation with red and white patches with ulceration
- **Hairy/Coated Tongue**
  - Lengthening of the tongue "hairs" (papillae) with bacterial coating resulting in thick white/brown/ black coating of the top of the tongue
- **Desquamative gingivitis**
  - Red, swollen, bleeding gums - not related to bacteria/dental plaque
- **Xerostomia**
  - Dry mouth

Oral problems caused by chronic GVHD cont'd

- **Angular cheilitis and exfoliative cheilitis**
  - Red and swollen lips with surface crusting and continuous peeling of the lips
- **Recurrent superficial mucoceles**
  - Clear, bluish or pink blisters in the roof of the mouth
- **Trismus**
  - Limited ability to open, due to scarring of the skin
- **Oral squamous cell carcinoma/leukoplakia**
  - Mouth cancer and precancer

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Lichenoid mucositis and keratosis
(swelling and sores in the mouth)

Reticular and plaque forms:

- Most common type
- Lacey white lines with focal white patches and raised plaques
- Typically painless; may feel rough on the surface

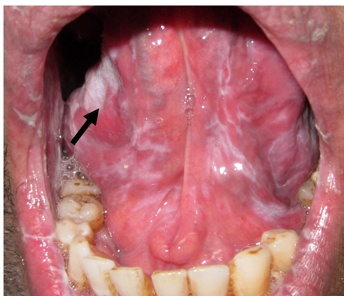
Erosive type:

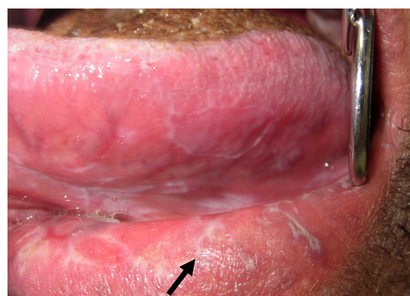
- Raw, scraped, red areas with faint subtle white lines in the peripheral areas; thinning of the mucous membrane (mucosa)
- Painful; burns while eating spicy, acidic or coarse food or drinking hot beverages.

Ulcerative form:

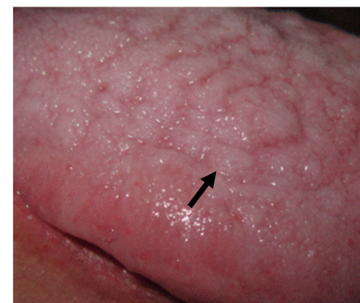
- Red area with central area of yellowish ulcer bed

Lichenoid keratosis (Mucosal thickening with callus)





Reticular variants on bottom and side surfaces of the tongue



Plaque variant on top of tongue

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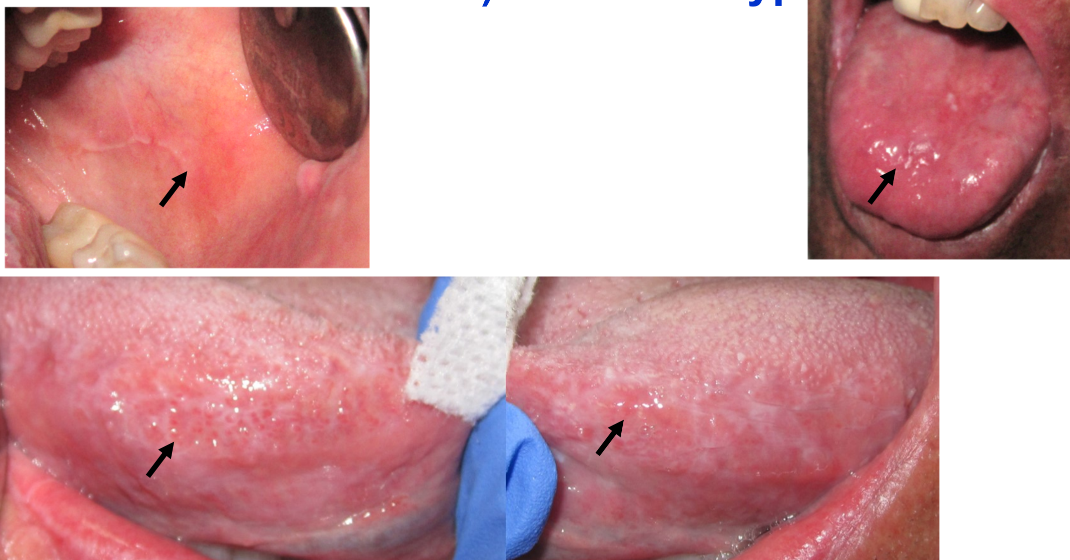
Lichenoid Mucositis (mouth sores with thinning of the mucosa) – Erosive Type



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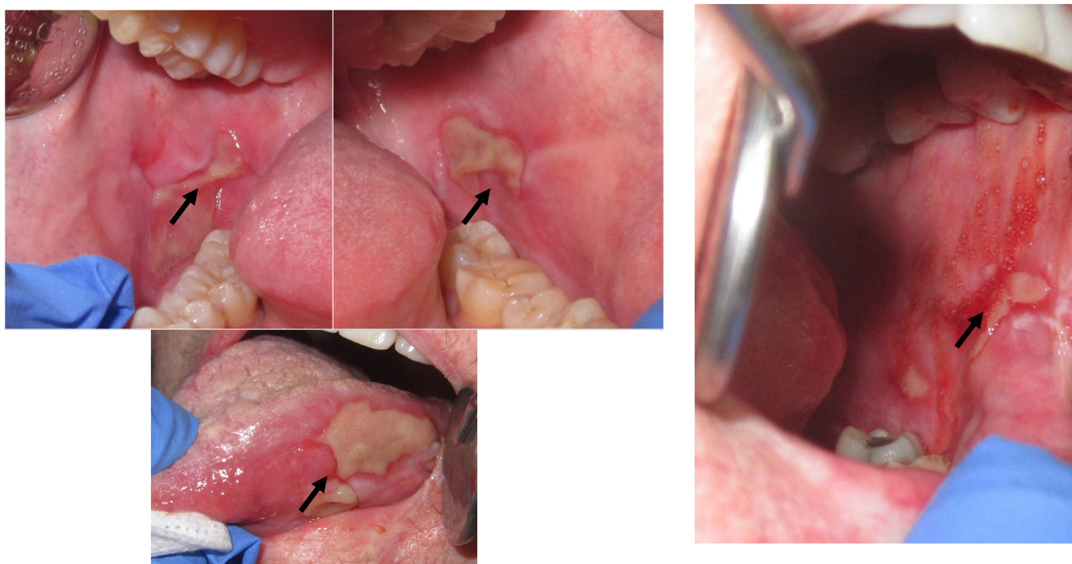
Lichenoid mucositis (mouth sores) – ulcerative type



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Treatment for Lichenoid Oral Sores

Treatment is warranted only if your mouth is hurting or burns while eating spicy or acidic food.

Treatment goal is to control the disease by reducing the amount of inflammation, thereby reducing pain and sensitivity.

1. Topical corticosteroids:
   - Clobetasol or Fluocinonide gel, 0.05%
   - Apply to the affected areas using cotton tip applicators; 2-4 times/day as needed; do not rinse your mouth, eat or drink for 30 minutes after each applications
   - These medications tubes may state “Not for internal use or For external use only.” However, these medications have been used for decades to treat oral sores in the mouth effectively.
   - These steroids are not FDA-approved for this use although there are many studies that demonstrate their effectiveness and safety for treating oral diseases.

Treatment for Lichenoid Oral Sores cont’d

2. Dexamethasone oral rinse (0.5 mg/5ml)
   - Used as a mouth rinse for patients with extensive oral sores or difficult to reach oral sore.
   - Take 1 teaspoon of solution, swish and hold in the mouth for ~ 5 minutes and spit out. Do not eat or drink for 15-30 minutes after each rinse.
3. Intralesional corticosteroid (Kenalog/ Triamcinolone Acetonide) injection:
   - For 1-2 large sores which are not healing with topical corticosteroid treatment.
4. Systemic corticosteroid treatment:
   - For severe and extensive sores in the mouth; Prednisone tablets or Dexamethasone oral solution, swish and swallow with gradual tapering doses.
5. Steroid sparing treatments:
   - Tacrolimus, either as an ointment for sores in the lips; or as a compounded rinse for oral sores.

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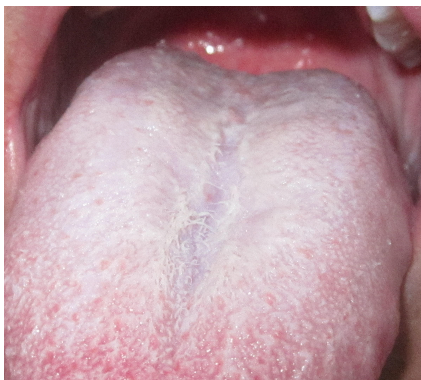
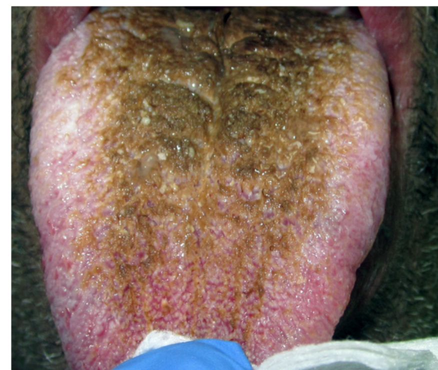
Treatment for Lichenoid Oral Sores

- If the topical gels or rinses causes stinging or burning, rinse your mouth with viscous lidocaine to reduce the pain caused by the gel or rinse.
- Frequent use of corticosteroid rinse in the mouth may cause yeast infection ("thrush") in your mouth, if you are not taking medications to prevent fungal infection.
- Anti-yeast (anti-fungal) medications such as nystatin, clotrimazole troches or fluconazole tablets are used for treatment.

Hairy/Coated Tongue





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Hairy/Coated Tongue

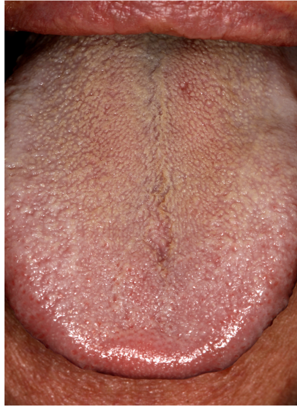
- Occurs on top of the tongue.
- Caused by lengthened “hairs” (papillae) with bacterial coating on the tongue.
- Coating appears white and can be mistaken for thrush.
- Coating may become stained black or brown by tobacco and food or by bacteria produced pigments.
- Frequently no symptoms other than cosmetic concern
- **Rare symptoms**:
  - Long papillae cause an irritating or gagging sensation
  - Unpleasant, stale or abnormal taste in mouth
  - Mouth feels dry

Hairy/Coated Tongue

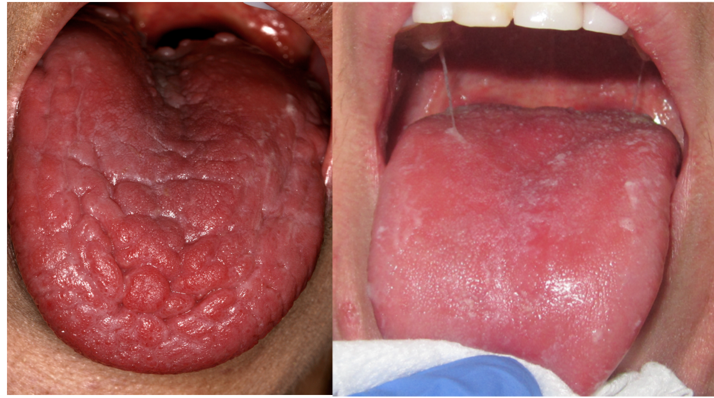
- Causes tongue “hairs” (papillae) to stick together longer than they should, rather than shedding, facilitating bacterial overgrowth and a shift in normal oral flora.
- Who are at risk of developing coated/hairy tongue?
  - Severely ill and hospitalized patients
  - Long-term treatment with antibiotics, chemotherapy or corticosteroids
  - Smoking
  - Use of strong, alcohol-containing or dehydrating mouth rinse
  - Dry mouth with thicker, less watery saliva

Coated tongue should not be mistaken for yeast infection/thrush

Coated (hairy tongue



Candidiasis (Yeast infection/Thrush)



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Treatment for hairy/coated tongue

- Maintain good oral hygiene
- Eliminate underlying contributing factors: Dry mouth etc.
- Use toothbrush or tongue scraper soaked with chlorhexidine or diluted (0.125%) Dakin solution; brush the tongue

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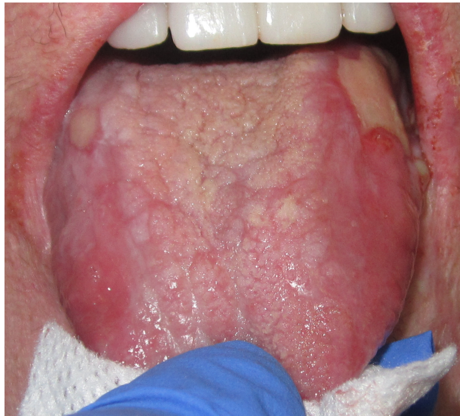
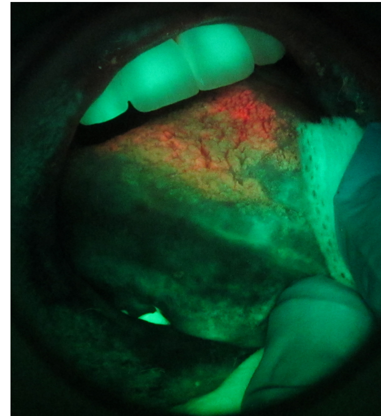
Dry mouth with thicker, less watery saliva





Decreased saliva (hyposalivation)

- Saliva normally lubricates the mouth and helps prevent infections and promotes healing of injured oral tissue
- Chronic GVHD causes “Sjogren syndrome”-like injury to salivary glands, causing decreased production of saliva
- Other causes of dry mouth in patients with GVHD:
  1. Drugs used for treating GVHD
  2. Disease related chronic anxiety or depression
  3. Dehydration

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Symptoms of decreased saliva production

- Sensation of a dry mouth, with or without noticeable, measurable decrease in the amount of saliva in the mouth
- Mouth feels parched, like sandpaper, all the time
- Tongue and lips stick to teeth
- Burning sensation while eating spicy or acidic food
- A bitter or metallic taste, or no taste
- Difficulty talking, chewing food and swallowing food (feeling of food getting stuck in the throat)

Additional complications from decreased saliva production

- Mouth discomfort
- Tooth decay
- Gum disease (gingivitis)
- Oral yeast infection
- Loss of or altered taste
- Oral ulcers

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Treatment for decreased saliva production

- Saliva substitutes, stimulants, sialagogue therapy (pilocarpine)
- Prevention of cavities – brushing/flossing/diet – fluoride
- Fluoride prescription gel
- Varnish – re-mineralizing agents
- Routine dental visits – bitewing radiographs – caries control
- Antifungal therapy for recurrent yeast infections

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Treatments for Dry Mouth – Over the Counter

- Biotene dry mouth toothpaste and mouth wash
- Mouth Kote Oral Moisturizer spray bottles
- Biotene oral balance gel and spray
- **Xylimelts®**
- Sparks Xylitol candies

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Treatments for Dry Mouth – Prescription

- NeutraSal
- Salivamax
- Cevimeline HCL (Evoxac®)
- Pilocarpine (Salagen®)

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Oral candidiasis ("thrush"): Most common oral yeast infection

- Burning or soreness in mouth and throat
- White-yellow curd-like patches
- Red, raw areas on the tongue and roof of the mouth.
- Patients with removable dentures are more susceptible.
- Angular cheilitis:
  - Corners of the mouth have red raw fissures that are sore and easily bleed when the mouth is opened wide
  - Lips can become chapped, red, peeling and swollen

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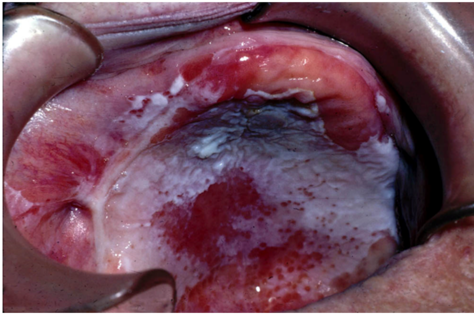
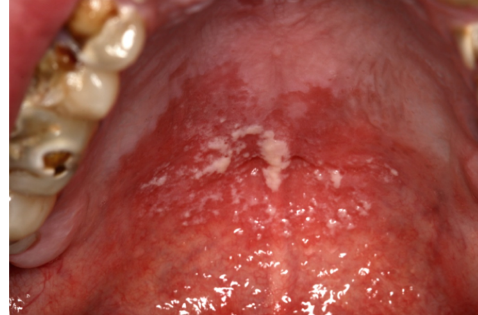
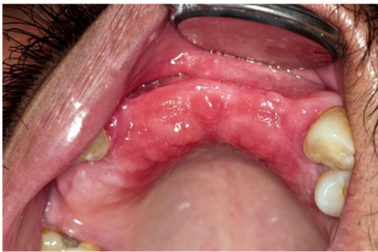
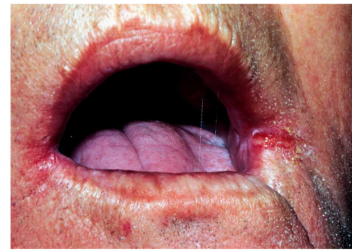
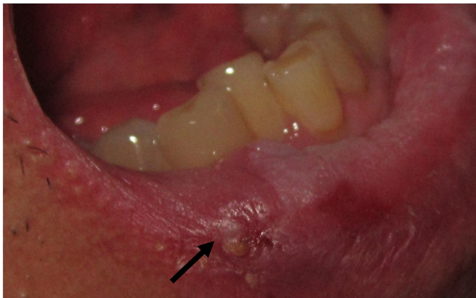
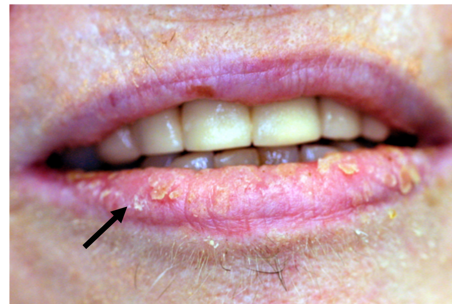
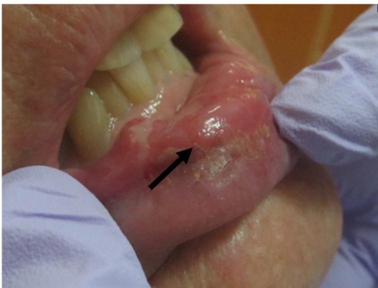
Oral candidiasis ("thrush") and angular cheilitis

Cheilitis with non-healing ulcer

Chronic GVHD patient with exfoliative cheilitis (chapped lips):

- Continuous peeling of the lips
- Red and swollen lips;
- Bacterial (Staphylococcus aureus) or yeast infection (Candida albicans)
- Systemic antimicrobial treatment may not be effective because bacteria and yeast colonize the dead skin/tissue without blood supply.
- Need to use topical antimicrobial treatment with or without topical corticosteroid to reduce the inflammation

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Local causes for infections inside and in the corners of the mouth

- Use of topical corticosteroid gels and rinses for oral GVHD or corticosteroid inhalers for asthma etc.
- Chronic dry mouth.
- Poor denture hygiene:
  - not removing the denture while sleeping
  - yeast may live on the denture surface.

Systemic causes of infections inside and in the corners of the mouth

- Long term use of use of antibiotics
- Due to an underlying medical condition
- Cancer/Leukemia or cancer treatment
- Taking immunosuppressive medications such as prednisone
- Poorly controlled diabetes

Topical treatment for oral candidiasis

- Nystatin oral suspension:
  - rinse and hold for 5 min and then swallow
  - 4-5 x day for 2-weeks
- Clotrimazole troches (10 mg):
  - Hold in the mouth and suck on the troches
  - 5x day for 2-weeks
- Local effect
- Needs to remove the dentures while using these medications

Systemic treatment for oral candidiasis

Fluconazole 100 mg:

- 1 tab/day for 2-weeks
- May cause drug interaction if you are taking the following medications
  - Blood thinners
  - Cholesterol medications
  - Seizure medications
  - Certain blood pressure medications

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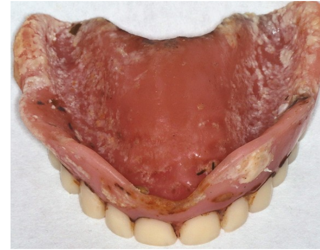
Treatment for yeast infection in the corners of the mouth and under denture plates

1. Mycolog II (nystatin/triamcinolone) cream
2. Lotrisone (clotrimazole/betamethasone dipropionate) cream
3. Vytone (iodoquinol/hydrocortisone) cream

Apply to the corners of your mouth 3-4 times x day for 2-weeks (angular cheilitis) or to the underside of your denture (denture stomatitis caused by yeast infection).



- Do not wear dentures while sleeping
- Disinfect acrylic dentures:
  - Soak the denture in sodium hypochlorite (1%) for 10 minutes.
  - Subject the denture for microwave irradiation (800 W) immersed in water for 6 minutes

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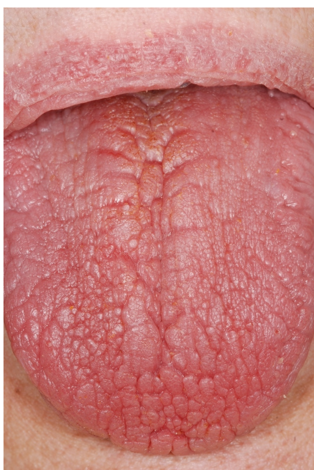
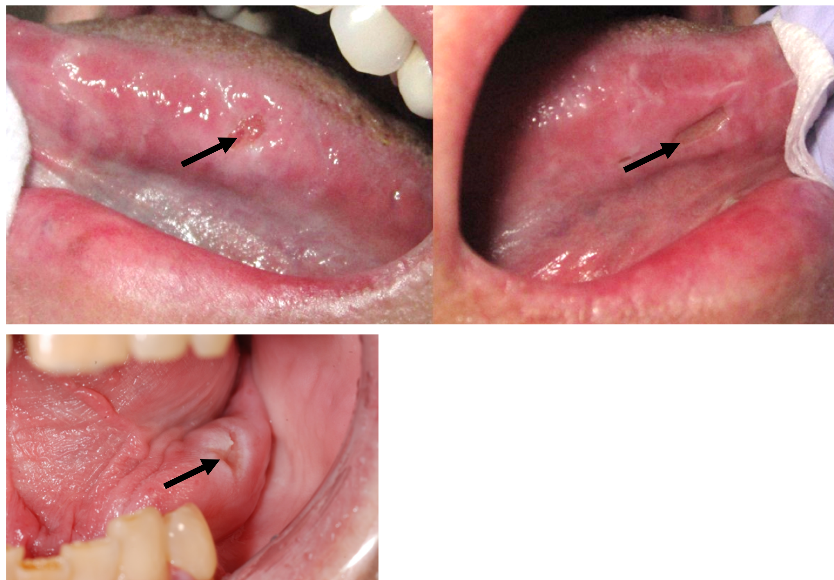
Dry mouth and ulcers





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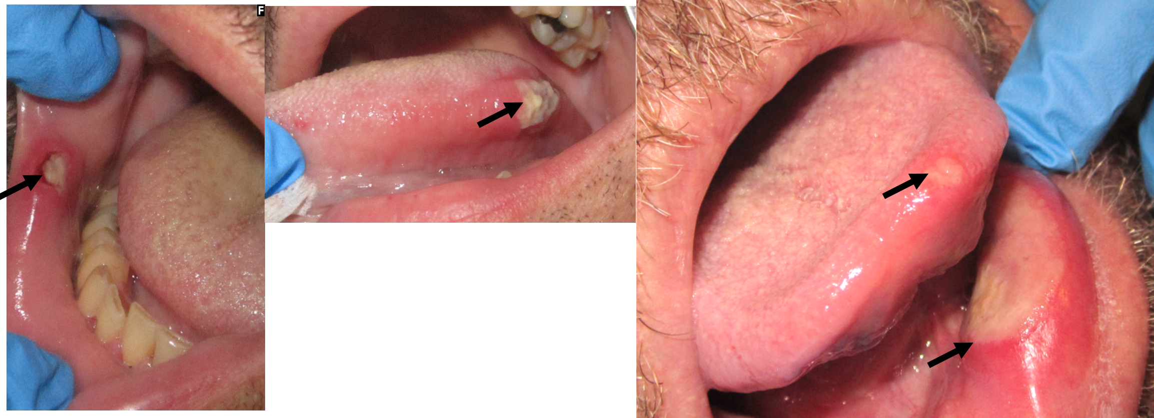
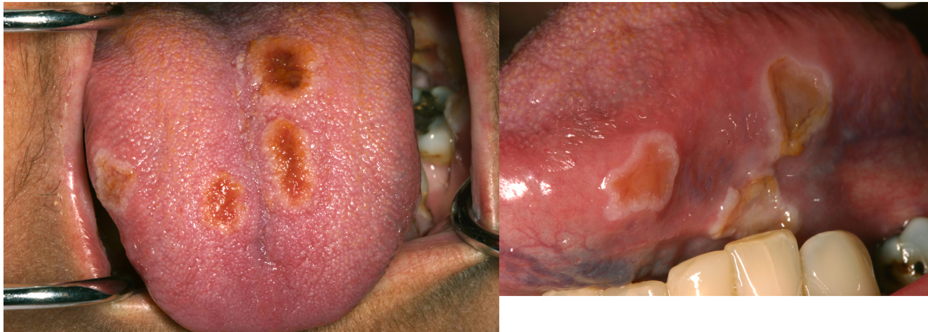
Nonhealing oral ulcers: Secondary bacterial infection with dead tissue



Non-healing (> 4- weeks) painful ulcers in the mouth

1. Traumatic ulcerative granuloma with eosinophilia (TUGSE)
2. Oral ulcers due to neutropenia (low white blood cells in the blood)
3. Ulcers caused by chronic herpes infection
4. 4. Oral cancer



- Chronic herpetic ulcerations can occur even if the patient is on anti-viral prophylaxis (i.e. Valacyclovir), due to rare drug resistant herpes virus
- Prevalence of drug resistant herpes virus among allogeneic transplant patients: 30%
- Diagnosis: Biopsy/Culture
- Treatment: Foscarnet, in consultation with an infectious disease physician; Kidney toxicity

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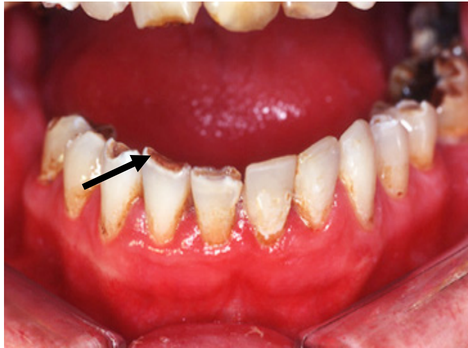
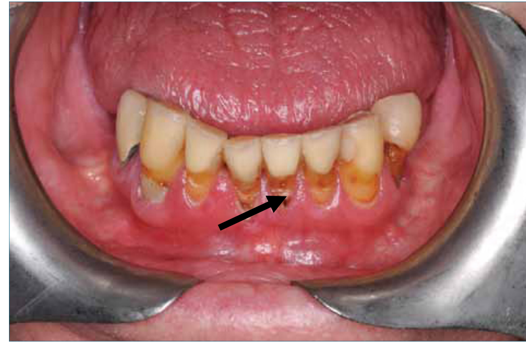
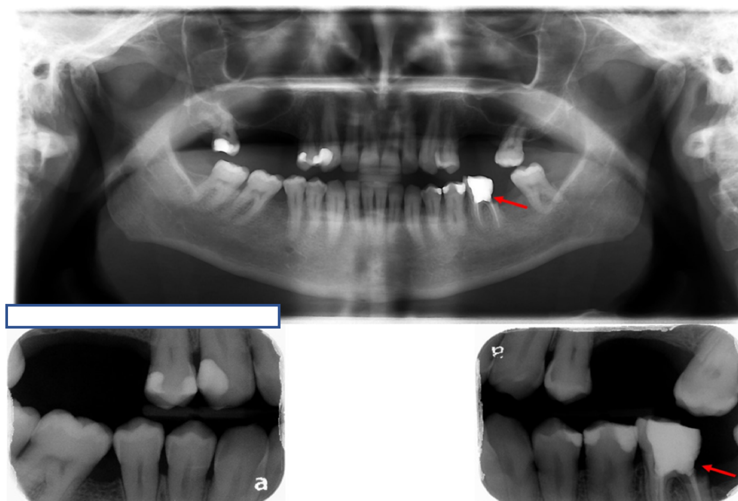
Dry mouth caused by GVHD increases risk of tooth decay at the level of the gums (cervical) and tip of the teeth (incisal)





Dry mouth caused by GVHD increases risk of tooth decay at the level of the gums (cervical) and underneath crowns



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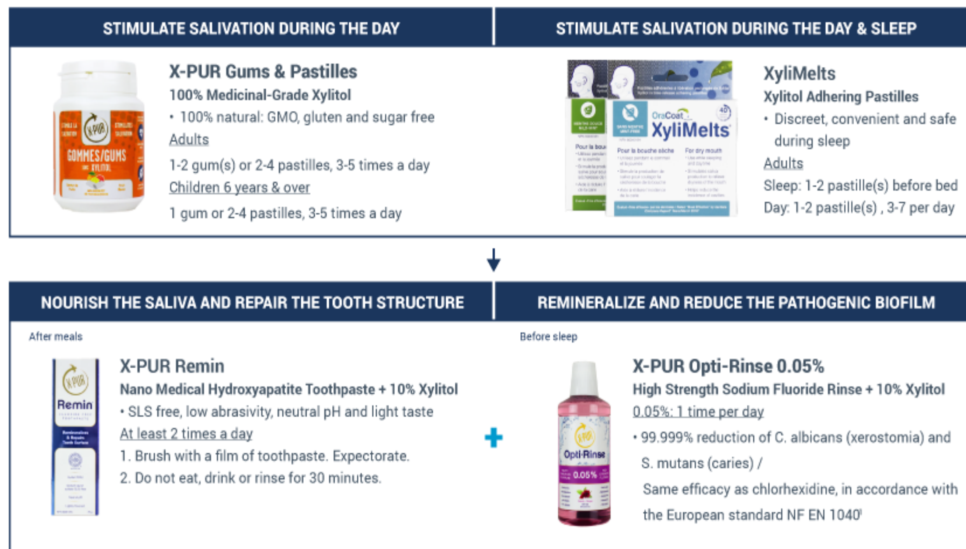
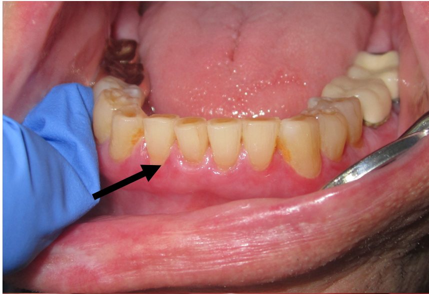
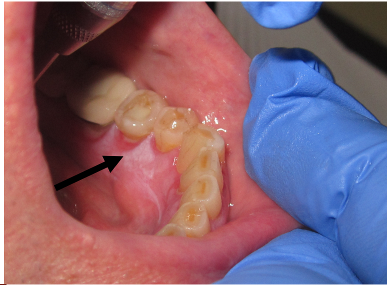
Prevent tooth decay (caries) due to dry mouth

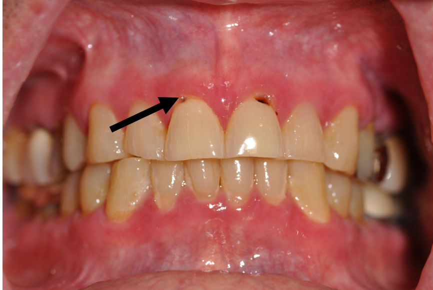
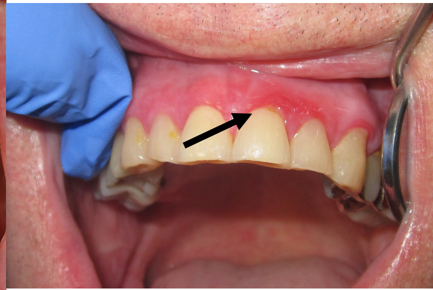
Prevent tooth decay (caries) due to dry mouth



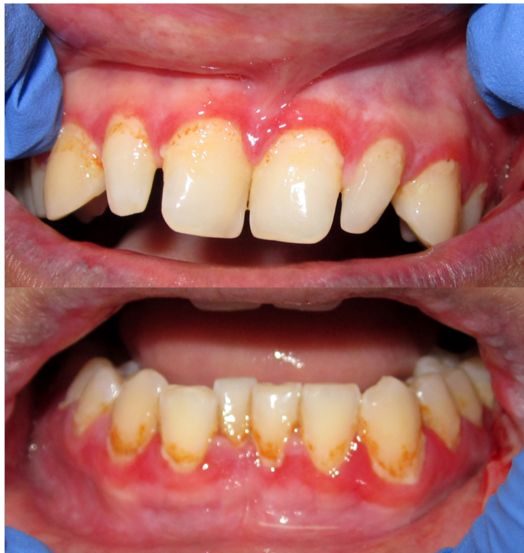
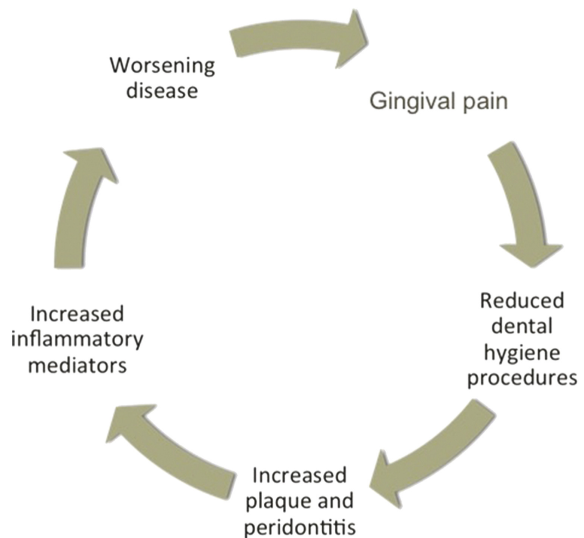
Gum sores (non-bacterial/plaque gingivitis)

- Gums are red, sore, shedding and bleed while brushing
- Dentists may mistakenly diagnose these gum sores are plaque-related

Gingivitis Cycle: Immune mediated-Plaque related

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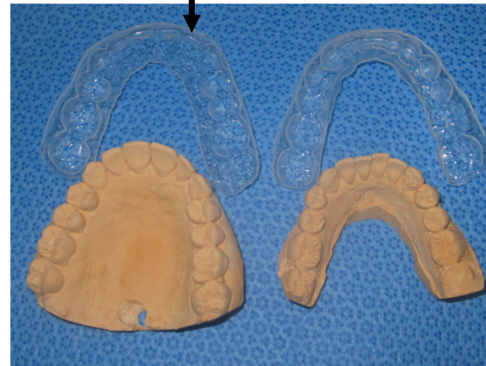
Treatment for Gingivitis caused by GVHD

Topical corticosteroid gel applied using medication application trays



Treatment for Gingivitis caused by GVHD cont'd

- Plaque control:
  - frequent teeth cleaning
  - use of soft toothbrush or electric toothbrush
- Use milder toothpaste like X, Y or Z
- Avoid tartar control/teeth whitening toothpastes

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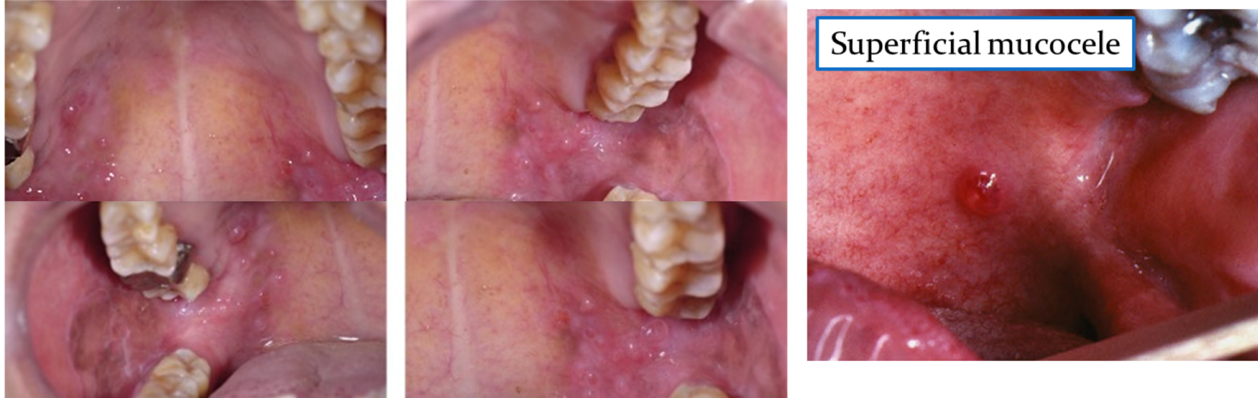
Fluid filled sores (mucoceles) on palate due to GVHD



Vesicles spontaneously rupture and leave small ulcers which heal in <2-3 days.

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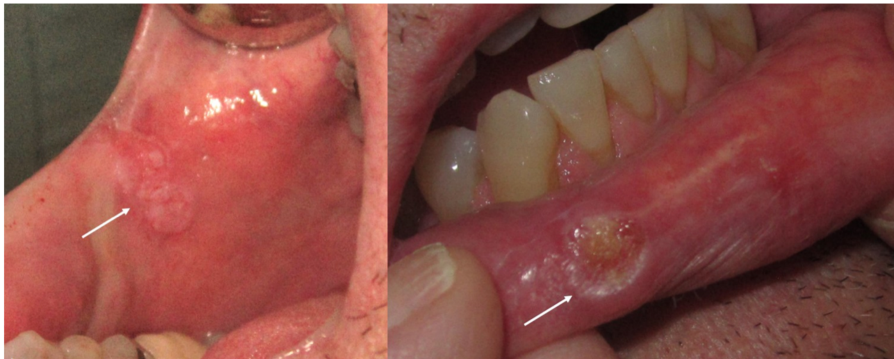
Increased risk for oral cancer after oral GVHD

2-6% of patients transplanted with donor cells (allogeneic stem cell transplant) develop cancer in the mouth 10-years after transplant



Oral cancer originates from the squamous cells that line the mucosal surfaces of the oral cavity. These tumors are referred to as Oral Squamous Cell Carcinoma (OSCC).

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How to Reduce the Risk of Developing an Oral Cancer

- Patients with oral cGVHD should undergo an oral cancer screening at least once a year.
- Oral cGVHD and other benign non-healing oral ulcers may mimic oral cancer.
- Hence, cGVHD patients should undergo annual oral cancer screening by a specialist who is familiar with both oral lesions of cGVHD, oral cancer and its precursors.
- Periodic biopsies of suspicious lesions are necessary.
- If you have a non-healing oral sore, new white or red patch, you should get these lesions checked up by oral medicine specialist.

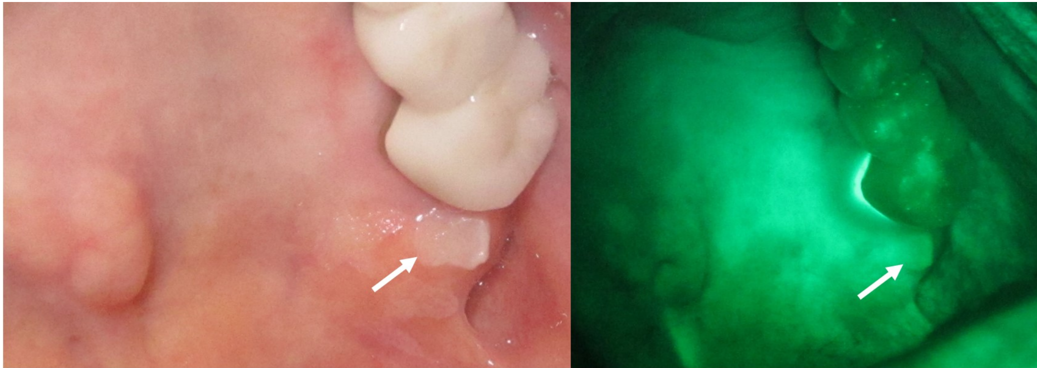
Oral Cancer Screening

A dentist or medical doctor will examine the oral cavity under white light looking for abnormal areas, including areas of leukoplakia (white patch) and erythroplakia (red patch) or non-healing sores.

The following procedures may be used to determine the risk of the oral lesion being precancer or cancer.

1. Autofluorescence visualization: A procedure in which lesions in the mouth are viewed using a special light.
2. Brush biopsy: The removal of cells using a brush that is designed to collect cells from all layers of a lesion. The cells are viewed under a microscope to find out if they are abnormal.
3. Scalpel biopsy: Confirmatory for diagnosing for oral cancer and precancer.

White plaque (leukoplakia) formation due to GVHD



White light   VELscope: Autofluorescence

- Leukoplakia: A white plaque that does not conform clinically or histologically to any specific disease
- Precancerous; needs to be biopsied for a definitive diagnosis
- Autofluorescence visualization using VELscope can help for risk-assessment

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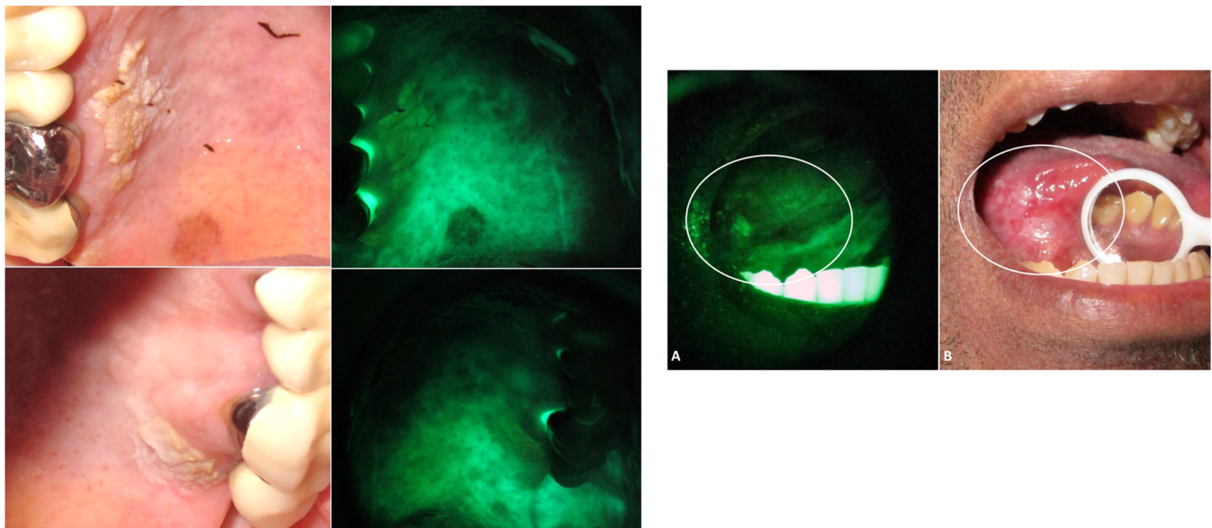
Plaque on palate and tongue due to GVHD



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Questions?

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