How I Treat Oral Chronic Graft-vs-Host Disease

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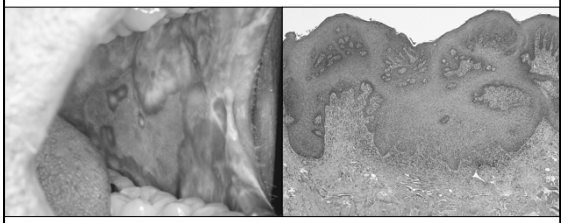
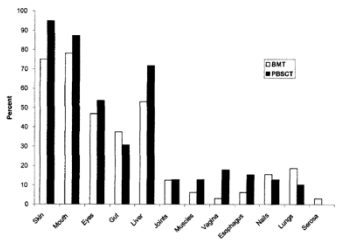
- No disclosures
- Includes off-label use of FDA approved medications

Learning Objectives

1. Define the clinical features of oral chronic graft-versus-host disease (cGVHD) and describe how it is diagnosed and monitored over time
2. Explain the pharmacologic principles of managing oral cGVHD and how to screen for potential complications



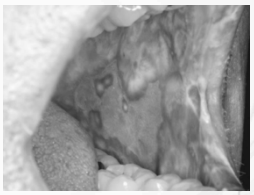
Oral cGVHD is very common

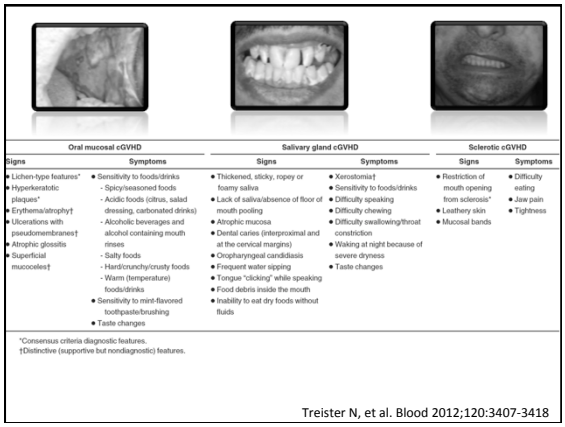


Flowers M, et al. Blood 2002;100:415-419

Oral cGVHD features

- Resembles immune/ autoimmune conditions
  - lichen planus
  - Sjögren syndrome
  - scleroderma
- Diagnosis primarily clinical
  - may be initial site
- Frequently refractory to systemic therapy
  - *important role for ancillary therapies*
- Increased oral cancer risk

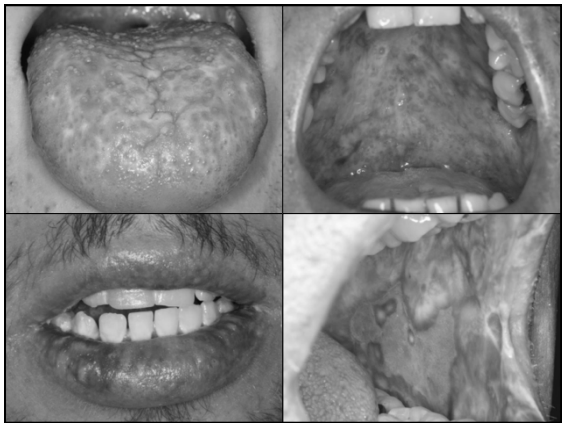




Oral mucosal cGVHD		Salivary gland cGVHD		Sclerotic cGVHD	
Signs	Symptoms	Signs	Symptoms	Signs	Symptoms
• Lichen-type features* • Hyperkeratotic plaques* • Erythema/atrophy† • Ulcerations with pseudomembranes† • Atrophic glossitis • Superficial mucoceles†	• Sensitivity to foods/drinks - Spicy/seasoned 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



Salivary gland cGVHD

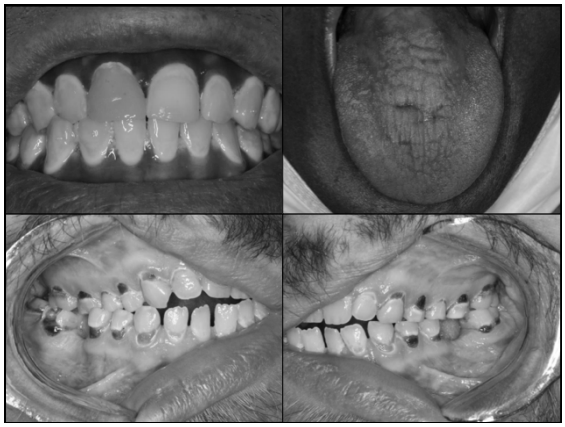
- Pathophysiology
  - lubrication/mastication
  - antimicrobial
  - buffering/remineralization
  - hypofunction/dysfunction
- Clinical features
  - xerostomia/pain/discomfort
  - difficulty eating/swallowing
  - dental caries
    - cervical, interproximal
  - recurrent candidiasis

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), 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

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

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



ARS #1

- According to the NIH criteria, which of the following is a diagnostic sign for oral chronic graft-versus-host disease?
  a. Erythema
  b. Ulcerations
  c. Lichenoid changes
  d. Superficial mucoceles
  e. Atrophic glossitis

How do we evaluate oral cGVHD?

- Chronic GVHD Oral Cavity Severity Score

Score 0	*Score 1*	*Score 2*	*Score 3*
No symptoms	Mild symptoms with disease signs but *not* limiting oral intake significantly	Moderate symptoms with disease signs with *partial* limitation of oral intake	Severe symptoms with disease signs with *major* limitation of oral intake

- Chronic GVHD Activity Assessment – Patient Self Report
  - *Severity over last 7 days*

	0	1	2	3	4	5	6	7	8	9	10
Your **mouth dryness** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
Your **mouth pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
Your **mouth sensitivity** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Filipovich A, et al. Biol Blood Marrow Transplant 2005;11:945-56

Table 3. Guidelines for management of oral cGVHD

	Treatment	Considerations
Oral mucosal cGVHD	Generalized disease ● Dexamethasone solution 0.5 mg/5 mL, 5 mL swish 5 minutes and spit, 2-4 times/day ● Clobetasol 0.05% solution ● Budesonide mouthwash (3 mg/10 mL) ● Tacrolimus 0.1% solution Focal disease (eg, solitary painful ulcers) ● Fluocinonide 0.05% gel, 2-4 times/day ● Clobetasol 0.05% gel, 2-4 times/day ● Intralesional triamcinolone therapy Lips ● Tacrolimus 0.1% ointment, 2-4 times/day	Instruct patients to wait 10-15 minutes after topical therapy before eating/drinking Gels can be applied with gauze and left in place 10-15 minutes Solutions: begin with dexamethasone, if inadequate response after 2-4 wks (4 times a day), substitute with clobetasol (budesonide can also be used). If after 2-4 wks still inadequate control, add tacrolimus and use equal parts with clobetasol as a single combined rinse Secondary candidiasis, typically occurs in first week, in addition to treatment most will require prophylaxis. Prophylaxis regimens include daily topical antifungal therapy or fluconazole 200 mg once/wk
Salivary gland cGVHD		
Xerostomia	Salivary stimulants (gum/candy) Oral-moisturizing agents Sialogogue therapy ● Pilocarpine 5 mg 3 times a day ● Cevimeline 30 mg 3 times a day	Sugar-free or xylitol-containing gum/candy Sialogogues may take 8-12 wks for full efficacy Avoid sialogogues in patients with pulmonary disease
Dental caries	Good oral hygiene Avoid sugary foods/drinks Topical fluoride therapy Remineralization therapy Regular dental visits	See Table 4 for detailed guidelines
Candidiasis	Fluconazole Disinfect removable prosthesis nightly	Topical steroid therapy increases risk of candidiasis Antifungal prophylaxis for recurrent candidiasis
Sclerotic cGVHD	Physical therapy Intralesional steroid therapy Surgery to disrupt mucosal bands	Condition is generally progressive and requires ongoing therapy

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

Management of mucosal cGVHD

- Topical corticosteroids
  - General considerations
  - Gels
    - clobetasol 0.05%
    - fluocinonide 0.05%
  - Solutions
    - 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
- (systemic)

Class 1—Superpotent

Betamethasone dipropionate 0.05% optimized vehicle
Clobetasol propionate 0.05%
Diflorasone diacetate 0.05%
Fluocinonide 0.1% optimized vehicle
Flurandrenolide 4 mcg/cm2
Halobetasol propionate 0.05%

Class 2—Potent

Amcinonide 0.1%
Betamethasone dipropionate 0.05%
Desoximetasone 0.25%
Desoximetasone 0.05%
Diflorasone diacetate 0.05%
Fluocinonide 0.05%
Halcinonide 0.1%
Mometasone furoate 0.1%

Class 3—Potent, upper midstrength

Amcinonide 0.1%
Betamethasone dipropionate 0.05%
Betamethasone valerate 0.1%
Diflorasone diacetate 0.05%
Fluocinonide 0.05%
Fluticasone propionate 0.005%
Triamcinolone acetonide 0.5%

Class 4—Midstrength

Betamethasone valerate 0.12%
Clocortolone pivalate 0.1%
Desoximetasone 0.05%
Fluocinolone acetonide 0.025%
Flurandrenolide 0.05%
Hydrocortisone probutate 0.1%
Hydrocortisone valerate 0.2%
Mometasone furoate 0.1%
Prednicarbate 0.1%
Triamcinolone acetonide 0.1%

Class 5—Lower midstrength

Betamethasone dipropionate 0.05%
Betamethasone valerate 0.1%
Fluocinolone acetonide 0.025%
Fluocinolone acetonide 0.01%
Flurandrenolide 0.05%
Fluticasone propionate 0.05%
Hydrocortisone butyrate 0.1%
Hydrocortisone valerate 0.2%
Prednicarbate 0.1%
Triamcinolone acetonide 0.1%
Triamcinolone acetonide 0.025%

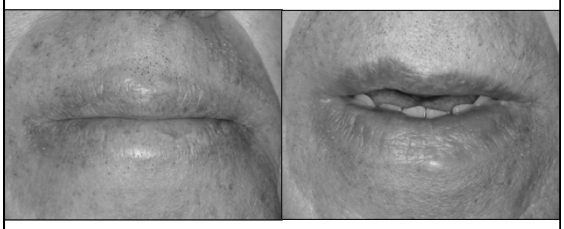
Class 6—Mild strength

Alclometasone dipropionate 0.05%
Desonide 0.05%
Fluocinolone acetonide 0.01%
Triamcinolone acetonide 0.025%

Class 7—Least potent

Topicals with **dexamethasone**, flumethasone, hydrocortisone, methylprednisolone, prednisolone

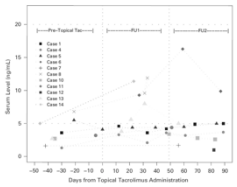
- **formulation/vehicle**
- **method/frequency of administration**
- **individual variability**



topical tacrolimus 0.1% ointment

Topical dexamethasone/tacrolimus

- N = 14
  - evaluated 49-86 days after starting therapy
- Oral symptoms improved
- Clinical scores stabilized/improved
- Well-tolerated, safe



Mawardi H, et al. Bone Marrow Transplant. 2010 ;45:1062-7

Protopic for pediatric oral cGVHD

- 6 children, no prior topical therapy
  - systemic therapy stable ≥ 2 wks
- Protopic 0.1%
  - 0.3-0.5 g/gauze, 15 m, BID
- Response in 6/6
  - CR (2), VGPR (2), PR (2)
  - 2-4 weeks to best response
- Safety
  - systemic levels in 4/6
    - most < 5.0 ng/mL
  - no renal toxicity

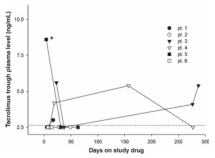
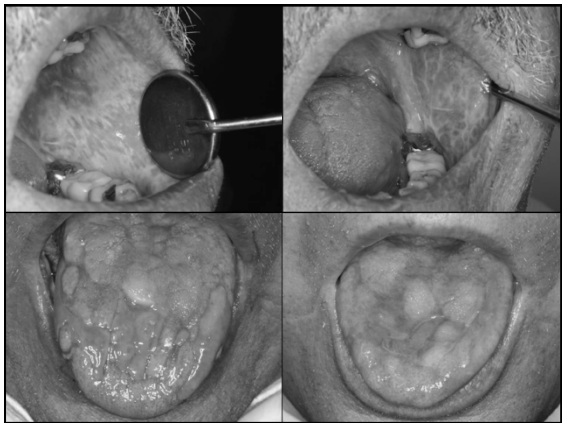


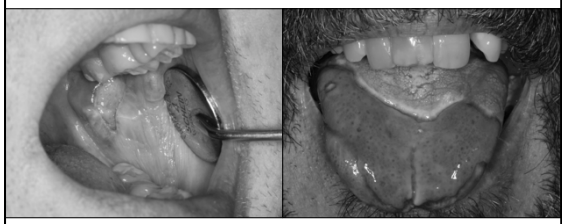
Fig. 1. Tacrolimus trough plasma levels. Plasma levels of tacrolimus were measured before the morning application of tacrolimus ointment at various time points starting one wk after study entry. *Measured after erroneous overdosage. The dotted line indicates the lowest detection level of the test used.

Albert M, et al. Pediatr Transplantation 2007;11:306–11



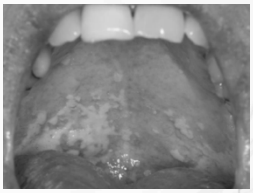
Intralesional steroid therapy

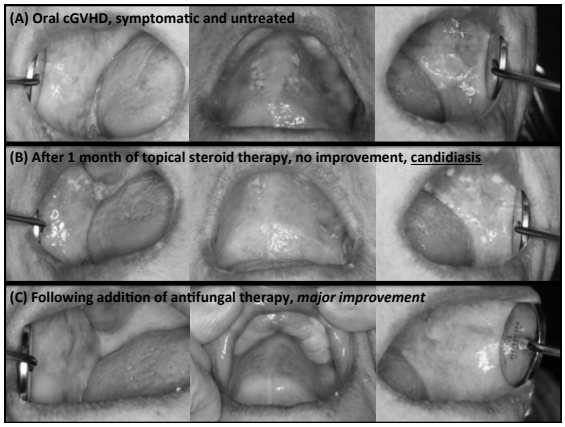
- Triamcinolone acetonide
  - 10, **40** (mg/mL)
- Locally intensive dose
  - large, painful, non-healing ulcers
- Procedure
  - shake vial, wipe clean
  - draw 0.1-0.2 cc/cm^2
  - inject under ulcer, quick delivery
- Multiple treatments often necessary

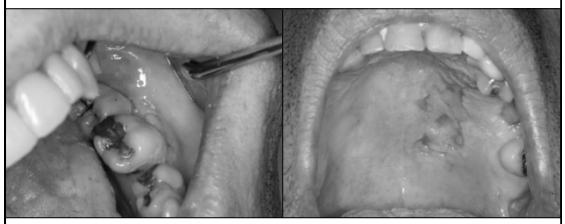


Infectious complications

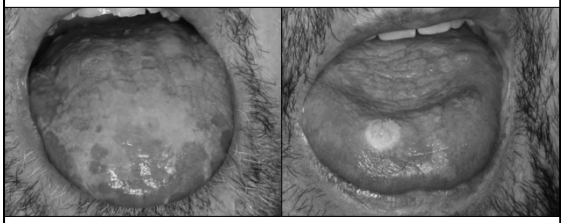
- Candidiasis
  - contributing factors
    - topical steroid therapy
    - immunosuppression
    - salivary gland dysfunction
  - Management
    - topical/systemic
    - short/long-term
- HSV recrudesence
  - immunosuppression
  - "breakthrough" infections
  - acyclovir/valacyclovir







recrudescent herpes simplex virus infection



Management of salivary cGVHD

- Saliva substitutes, stimulants, sialogogue therapy
  - pilocarpine/cevimeline
  - contraindications
- Caries prevention
  - brushing/flossing/diet
  - fluoride
    - prescription topical gel
    - varnish
  - remineralizing agents
- Routine dental visits
  - bitewing radiographs
  - caries control
- Recurrent candidiasis

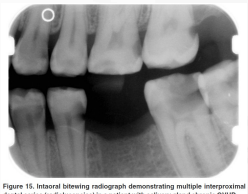


Figure 15. Intaoral bitewing radiograph demonstrating multiple interproximal dental caries (radiolucencies) in a patient with salivary gland chronic GVHD.

ARS #2

- Which of the following topical steroids has the greatest potency?
  a. Fluocinonide
  b. Dexamethasone
  c. Hydrocortisone
  d. Clobetasol
  e. Triamcinolone

Summary

- Oral cGVHD common, may be initial site
- Wide range of signs/symptoms
- Management
  - topical corticosteroids & tacrolimus
  - avoid irritating food/drink/toothpaste
  - salivary stimulants & moisturizing agents, sialogogues, fluoride, mild/child's toothpaste
- Oral cancer surveillance
  - differentiate from GVHD
- May require treatment for many years