

## Common Oral Conditions: Diagnosis and Treatment

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## Oral Disease Diagnosis

- Oral disease may be sign of systemic disease/systemic disease may present orally
- Most oral lesions appear similar clinically
- Oral symptoms may be vague
- Oral disease is extremely difficult to diagnose based on exam only
- Detailed history is essential

## Oral Mucosal Disease

- Acute or Chronic
- Single or Multiple
- Primary or Recurrent
- Local or Systemic

## Oral Mucosal Disease

- Infectious
- Immunologic
- Other

## Differential Diagnosis of Ulcerative Oral Mucosal Disease

	INFECTIOUS	IMMUNOLOGIC	OTHER
Acute Primary		Aphthous Ulcer	Traumatic ulcer
Single			
Acute		RAU	
Recurrent			
Single			
Acute Primary	HSV	Aphthous	
Multiple	Other viruses	Stomatitis	
Acute	RHL	RAS	
Recurrent	VZV	Erythema	
Multiple		Multiforme	
Chronic	Deep Fungal		Malignancy
Single	Infections		
Chronic		Erosive Lichen	
Multiple		Planus	
		Pemphigus	
		Pemphigoid	
		SLE	
		Allergy	

## Herpes Simplex I

- Primary vs. Recurrent
- Incubation days to 2 weeks
- Vesiculo - ulcerative eruption
- "Gingivostomatitis"
- 90% of the population has HSV antibodies
- Recurrent labialis vs. intraoral HSV
- 33% of the United States population experience recurrent herpetic lesions

## Herpes Simplex

- **Lab Diagnosis**
  - Cytology Tzanck - Giemsa stain
  - DFA HSV Antibody
  - Virus isolation via tissue culture
  - Antibody levels of acute and convalescent serum 4X increase

## Recurrent Herpes Simplex Latency and Reactivation

- **Labialis**
  - Reactivation not re infection 30%
  - Stimulated by stress/sun etc.
  - Can be on nose or other perioral area
  - Multiple coalescing vesicles or ulcers
  - Prodromal burning or tingling
  - Common
- **Intraoral**
  - Usually associated with immunocompromised patients
  - Can be on any intraoral site
  - Painful
  - Most common oral infection associated with chemotherapy

## Herpes Simplex Treatment

- Most cases are self-limiting, requiring only palliative care
- Consider systemic antivirals if within 48 to 72 hours of lesions and sig. disease
  - Acyclovir
  - Valacyclovir
  - Famciclovir / Penciclovir
  - Foscarnet

## ACYCLOVIR

- Converted by viral thymidine kinase to a form that inhibits viral DNA polymerase and replication
- Acute HSV II treatment dose: 200mg 5Xd for 10 days
- Suppression HSV II dose: 400mg bid for one year
- Must assess renal function
- Topical prep may decrease duration of viral shedding

## VALACYCLOVIR

- Indicated for HSV I treatment; HSV II treatment/suppression and VZV treatment
- TTP/ Hemolytic uremic syndrome has been reported in HIVD, BMT, and renal txplt patients in doses of 8 gm/d
  - Warning for use in immunocompromised population

## VALACYCLOVIR

- Recurrent HSV (labialis) treatment dose 2gm BID X 1 day
- HSV II treatment dose: 1gm bid 10 days
- Recurrent HSV II treatment dose: 500mg bid 5 days
- HSV II Suppressive therapy dose: 1 gm qd
- Must assess renal function

## FAMCICLOVIR

- Pro drug of penciclovir
- Indicated for recurrent HSV I in HIV patients, acute HSV II treatment and suppression
- Doses variable with disease

## FAMCICLOVIR

- HSV I (immuno-compromised)  
Recurrent treatment dose 500mg bid
- HSV II treatment 125mg bid;  
suppression 250mg bid

## Topical Prescription/OTC Antivirals

- Zovirax\*
  - \*Glaxo Wellcome
- Denavir\*
  - \* SmithKline  
Beecham
- Abreva\*
  - \*Avanir  
Pharmaceuticals

## Denavir 1%

- 5/8 of a day shorter duration than placebo
- specific HSV labialis indication
- q2h application while awake for four days
- decreases viral shedding

## Abreva 10%

- FDA approved as an OTC product for recurrent Herpes simplex
- Long chain alcohol active against lipid enveloped viruses
- Interferes with virus ability to enter target cells
- 5 times daily
- No significant systemic toxic effects in animals
- 18 hours shorter compared to placebo

## HERPES SIMPLEX Treatment

- To date, the FDA has not approved the use of systemic antiviral medications for oral HSV *suppression* in immunocompetent patients

## Recurrent Aphthous Ulcers I

- Acute, recurring, single or multiple ulcers
- Can be minor <1cm, major or herpetiform
- Precipitating factors include stress, trauma, food (SLS) allergies and hormonal alterations, cessation of smoking
- Iron, B12, folate deficiency in 5 - 15 % of patients
- Screen patients for anemia, IBS, and immunosuppression if started/worsened after age 25
- Can be associated with HIV, Reiter's, Crohn's, CTD, neutrophil dysfunction, granulomatous dz., Behcet's, gluten allergy

## Recurrent Aphthous Ulcers

- Work up based on ROS and can include labs, and biopsy

## Recurrent Aphthous Ulcers

- Painful ulcers, covered by a gray pseudomembrane surrounded by an erythematous halo
- Start as a papule
- Usually on "movable" oral mucosa
- 10 to 14 days of healing (no scar)

## Aphthous Stomatitis

- Associated with HLA B12, B51, and Cw7
- T - Cell lymphocytic infiltrate
  - elevated CD8+ / reduced CD4+ cells
  - results from antigenic challenge in response to cytokines that regulate lymphocytic trafficking
  - ICAM 1 expression in submucosal vasculature
- Increased NK cell activity
- Cytokine mediated toxicity IL2, INFg, TNF

## Aphthous Stomatitis: Treatment

- Discontinuing offending product
- Gluten free diet
- Trial SLS absent toothpaste
- ? effect of triclosan toothpaste
- Tetracycline rinses/paste
- L lysine; other vitamin supplements
- Palliative solutions
- Chlorohexidine gluconate .12%

## Aphthous Stomatitis: Treatment

- Treatment:
- Correct anemia
- Topical steroid application
- Amlexanox 5%

## **Aphthous Stomatitis: Treatment**

- **Systemic steroid preparations**
  - Medrol dose pack
  - Prednisone
- **Intralesional steroid injection:**  
Aristospan 5mg/ml
- **Pentoxifylline, colchicine, thalidomide**

## **TOPICAL STEROIDS**

- **Group 1- ultra high potency:**
  - - betamethasone dipropionate 0.05% (Diprolene)
  - - clobetasol 0.05% (Temovate)
- **Group 2- high potency:**
  - fluocinonide 0.05% (Lidex)
- **Group 3- medium potency:**
  - triamcinolone acetonide 0.5% (Aristocort)
- **Group 4- lower potency**

## **TOPICAL STEROIDS**

To increase effectiveness in mouth:

- **Gingiva – soft medication splints**
- **Mucosa – gauze pads**
- **Vehicle plays significant role in efficacy**

## **Amlexanox 5%**

- **76% median reduction in ulcer size compared to 40% placebo**
- **Overall mean reduction in ulcer size of 1.82 mm<sup>2</sup> vs. .52 mm<sup>2</sup>**
- **1.6 days sooner vs. no treatment**
- **Unknown but anti-inflammatory inhibitor of histamine/leukotrienes**
- **No significant side effects**
- **QID X 10 days**

## **PENTOXIFYLLINE**

- **Methylxanthine**
  - Caffeine, Theophylline
- **Used in PVD, ASCVD**
- **60% improvement in RAS**
- **400mg tid**
- **Nausea, vomiting, hypotension**

## **COLCHICINE**

- **Used in gouty arthritis**
- **70% improvement in RAS**
- **.5 to .6mg bid to tid**
- **Nausea, hepatotoxicity, decreased sperm count, aplastic anemia**

## THALIDOMIDE

- Major RAS
- HIV—RAS
- Dose 50mg/day
- STEPS program to be able to prescribe

### Side Effects

Severe, life threatening BIRTH DEFECTS

- Peripheral neuropathy
- Drowsiness
- G.I.

## Lichen Planus

- Chronic, multiple ulcerations
- Very common mucocutaneous disease
- Thought to be related to a cell mediated immune response involving Langerhan's cells, which stimulates the destruction of the basal cell layer of the epithelium
- Probable genetic predisposition

## Etiology of Lichen Planus

- Immune mediated - T cell mediated degeneration of the basal cell layer of epithelium
- associated with stress, drug hypersensitivity (lichenoid drug reaction), or infection (HCV)
  - NSAIDs, allopurinol, sulfonamides, tetracyclines, ACE inhibitors, HCTZ, lorazepam, sulfonylureas
  - dental materials
    - amalgam and resins
  - idiopathic

## Lichen Planus

- May be associated with stress, drug hypersensitivity (lichenoid drug reaction), or infections (hepatitis c)
- Drugs inducing a lichenoid reaction include NSAIDs, allopurinol, sulfonamides, tetracycline, ACE inhibitors, HCTZ, lorazepam, sulfonylureas
- Dental materials
  - Amalgam (mercury and metals), resins

## Lichen Planus

- Treatment: biopsy necessary to r/o SLE, pemphigoid, pemphigus and dysplasia.
- Topical, intralesional and systemic steroids
- Tacrolimus, CSA

## TOPICAL STEROIDS

To increase effectiveness in mouth:

- Gingiva – soft medication splints
- Mucosa – gauze pads
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## Lichen Planus

- Pre - malignant controversy ? Over!!!
- Appears approx. .4% - 2% per 5 year observation period 1.5% per 7.5 years
- Equates to those who have leukoplakia and represent some 50 times the rate of the general population

## Mucous Membrane Pemphigoid

- Formally known as "cicatricial pemphigoid"
- Usually seen in patients >50 years old
- Sub-epithelial vesicles/blisters
- Results in junctional separation
- One of many sub epithelial bullous dermatosis

## Pathogenesis of MMP

- Autoantibodies (IgG) against proteins in basement membrane zone, acting with complement (C3) and neutrophils cause subepithelial split and vesicle formation
- Ulcerative lesions on any mucosal surface
  - Labial, buccal, palate, and tongue
  - Skin involvement in 25%
  - Eye, esophageal, and tracheal involvement
- Diagnosis via biopsy for routine and immunofluorescent study

## Pemphigoid

- Older patients
- Desquamative gingivitis as well as other mucosal surfaces
- Scarring
- Ocular involvement
  - symblepheron
- Esophageal and tracheal strictures
- Must differentiate from ELP PV and SLE

## Mucous Membrane Pemphigoid

- Biopsy
  - Routine
  - DIF
  - IIF
    - Salt Split Skin Technique to uncover and expose the targeted antigens
    - Epidermal side lamina lucida BP
    - Dermal Side lamina densa Epiligrin
    - BP-MMP-EBA

## Pemphigoid III

- Treatments:
  - Topical steroid application
  - Systemic steroid preparations
  - 1-1.5mg/kg/day
  - Intralesional steroid injection
  - Dapsone
  - Tetracycline 500mg bid /Minocine 50-100mg/day
  - Nicotinic acid/ niacin/nicotinamide 2-2.5gm/day
  - Antimetabolite – azathioprine 1-2mg/kg/day

## Dapsone

- Used in infectious disease, inflammatory disease and dermatologic disorders
- Suppresses neutrophil function
- Interferes with myeloperoxidase
- Decreases neutrophil adherence to endothelium

## Dapsone

- Side Effects:
  - Hemolysis
  - G6PD deficient patients cannot tolerate
  - Formation of methemoglobin
    - Consider methemoglobinemia in fatigued patients with normal Hg levels
  - Dapsone hypersensitivity syndrome - serum sickness
  - Peripheral neuropathy
  - Requires blood tests monthly
- Side effects reduced with Vitamin E 400 units bid and cimetidine

## Dapsone Protocol

- Get G6PD screen
- Start 25 mg recheck Hg in 1 week
- Increase drug slowly 25mg q3days
  - Frequent Hg checks and ROS questions may need to stay at a level before increasing
- Effective dose 100mg to 200mg

## Tetracycline/Minocine

- Decrease leukocyte chemotaxis
- Associated with photosensitivity
- Interferes with BCP
- May interfere with coumadin
- GI symptoms
- Minocine associated with hyperpigmentation

## Nicotinic Acid

- AKA Niacin, Vitamin B2
- Inhibits neutrophil function – chemotaxis
- Associated with flushing
- Risk of myopathy in patients taking statin drugs

## Pemphigus V. Pemphigoid

Feature	Pemphigus	Pemphigoid
Circulating Ab	Yes, IgG	No
Tissue-bound auto-Ab	Yes, IgG, complement	Yes, IgG, IgA
Target tissue	Desmosomes	Lamina lucida
Vesicles	Intraepithelial	Subepithelial
Sites affected	Oral mucosa, skin	Oral mucosa, eye, genitals
Nikolsky's sign	Yes	Yes
Prognosis	Fair to Good	Good to excellent

## **Carcinoma**

- A single chronic oral lesion is cancer until proven otherwise
- Higher incidence in smokers and drinkers
- Various presentations
- Diagnosis is via biopsy
- Referral to Head and Neck surgeon

## **Epidemiology I**

- One of the 10 most common causes of death
- Accounts for 3% of the approximately 1 million new cancers diagnosed per year in the U.S.
- Males
  - 4% of total body cancers
- Females
  - 2% of total body cancers
- Majority of oral cancers are squamous cell carcinomas

## **Epidemiology II**

- 95 % of cases occur in patients over 40 years old
  - Average age of diagnosis is 60 years old
  - Increase in incidence in younger females
- Majority of oral cancers involve the following sites
  - Tongue
  - Oropharynx
  - Floor of mouth

## **Etiology**

- Incidence of oral cancer is age related
  - Declining immune surveillance with age
  - Accumulation of genetic changes
  - Duration of exposure to initiators and promoters
- Long term follow up of immunosuppressed patients showed increased risk of developing squamous cell carcinoma

## **Prognosis**

- TNM system of cancer classification
- OC occurring in the posterior aspect of the oral cavity and oropharynx is associated with a poorer prognosis
- Most important factor in survival is the stage of disease at diagnosis
- Incidence of spread is influenced by tumor size
- Localized tumors of the oral cavity and pharynx have an overall survival rate of 70%
- Patients with distant metastases demonstrated an overall survival rate of 33%

## **Pathogenesis I**

- Multistage process
- Premalignant lesion as defined by WHO
  - Morphologically altered tissue in which cancer is more likely to occur
- Oral leukoplakia
- Oral erythroplakia

## Pathogenesis II

- **Dysplastic lesions**
  - Mild dysplasia
    - Dysplastic cells are limited to the basal layer of the epithelium
  - Moderate / Severe dysplasia
    - Increasing cellular changes in cellular morphology in increasing thickness of epithelium
- **Carcinoma in situ**
  - Abnormal cells involve the entire epithelium without invasion through the basement membrane
- **Carcinoma**
  - Disruption of the basement membrane and invasion into connective tissue

## Management of Leukoplakia

- **Eliminate risk factors**
- **Therapy is indicated if leukoplakia displays dysplasia (possibly even those non dysplastic) upon biopsy**
  - Laser excision
  - Clinical Studies
    - Topical application of Vitamin A
    - Systemic retinoids

## Proliferative Verrucous Leukoplakia (PVL)

- **Verrucous form of oral leukoplakia**
- **High risk of progression to squamous cell carcinoma 70% +**
- **More common in males**

## Signs / Symptoms

- **Initially asymptomatic**
- **Most cases identified after development of symptoms and progression of disease**
- **Patients may have discomfort and / or be aware of a mass**
- **Difficulty with speech / swallow**
- **Careful assessment of lymph nodes**
  - Submandibular, digastric, upper cervical, cervical chain nodes
- **Careful assessment of oral tissues**

## Treatment

- **Choice of treatment depends on variety of factors**
  - Site / size / location of primary tumor
  - Lymph node status
  - Presence of bone involvement
  - Ability to achieve adequate surgical margins
  - Ability to preserve speech
  - Ability to preserve swallowing function
  - Physical / mental status of patient
  - Potential complications of each therapy