

# Recurrent Aphthous Stomatitis & Oral Herpes

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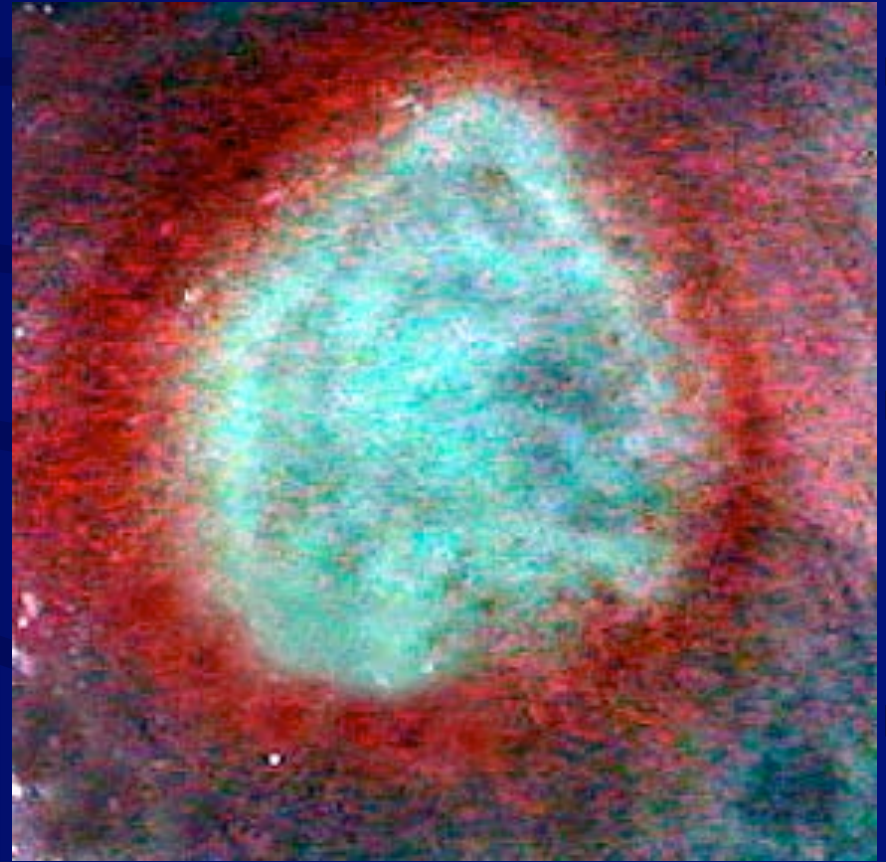
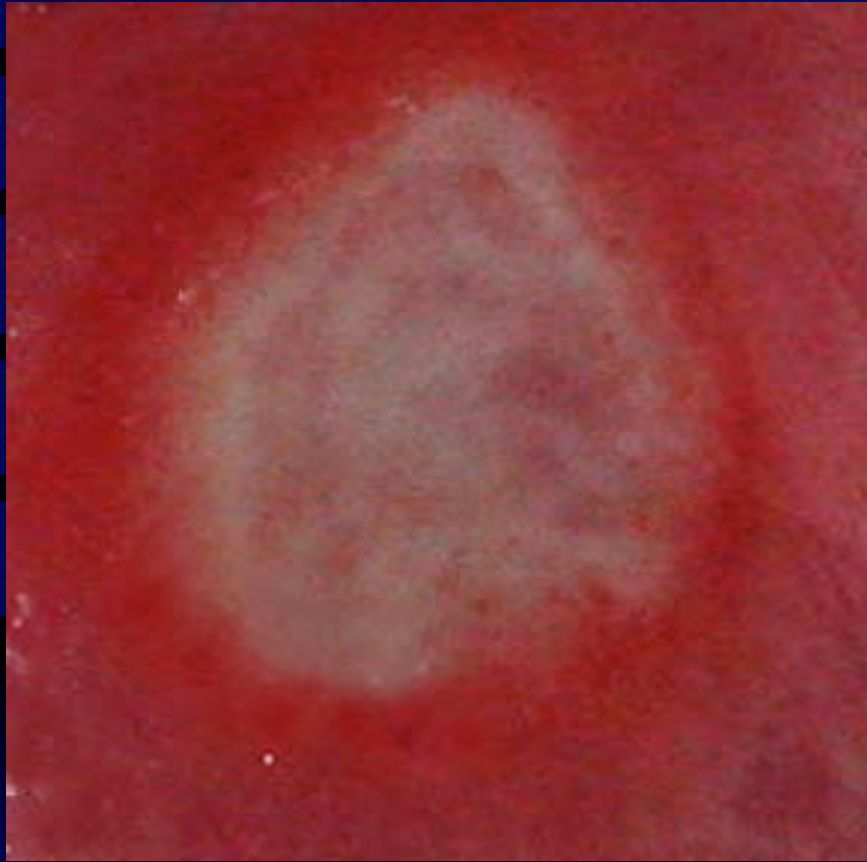
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# ΑΡΗΤΗΑΕ vs αφθαλι

Etymology: Oxford English Dictionary:

- [L. *aphtha* (in cl. L. always in pl. *aphthæ*), a. Gr. αφθα, mostly in pl. αφθαλι ; usually connected with απτ-εω - to set on fire, inflame.]



- Most common oral mucosal disorder.
- Polygenic mode of inheritance
  - >40% of RAS sufferers have 1<sup>st</sup> degree relatives with RAS.
- Acute and extremely painful recurring mouth ulcers usually involving non-keratinized oral mucosal sites.
- May interfere with eating, drinking, or swallowing.
- They may be classified as minor, major or herpetiform.

# Minor RAS

- “Canker sores”
- High prevalence: 5-25%
- 75-85% of all RAS cases
- <10mm in diameter
- Ulcer is shallow, round/oval, a yellow pseudomembrane with slightly raised margin and erythematous halo.
- Resolve without treatment in 7-14 days
- No scarring
- Recurrence rates vary



# Major RAS

- 10-15% all RAS cases
- >10mm in diameter
- Ulcer is deeper, often with irregular border
- Healing can take weeks or months
- May be associated with fever or malaise
- Predilection for the throat
- Often leaves scarring
- Recurrence rates vary



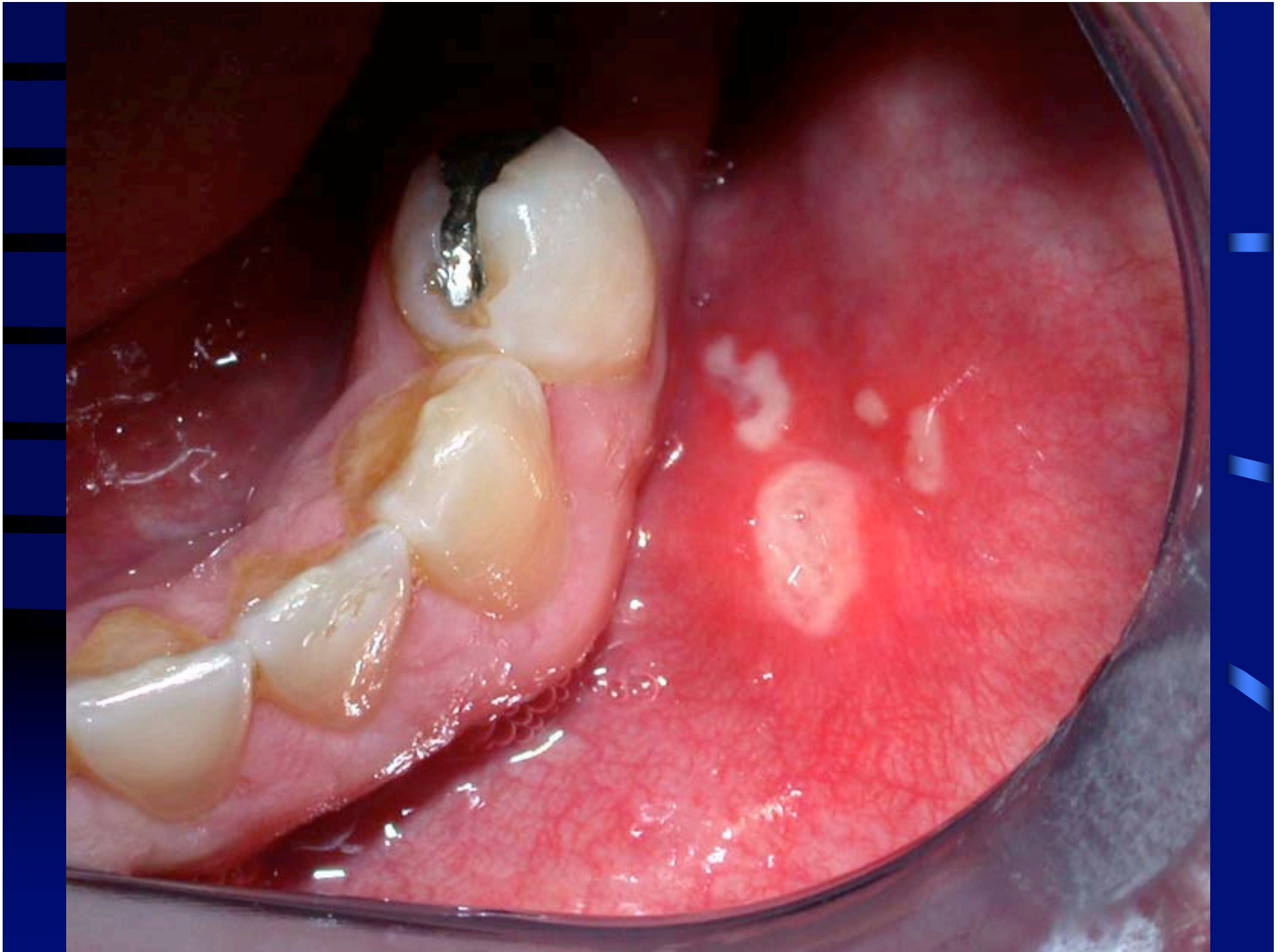




# Herpetiform RAS

- 5-10% all RAS cases
- Crops of ulcers <5mm in diameter which may fuse.
- Resolve without treatment in 7-14 days
- No scarring
- Recurrence rates vary





# Etiology ?

- Local/Oral Factors

- Trauma
- Salivary gland dysfunction

- Microbial

- Bacterial: streptococci
- Viral: human herpes 6, herpes simplex, cytomegalovirus, Epstein-Barr, varicella zoster

- Nutritional and Allergic Conditions

- Toothpaste allergies eg Sodium lauryl sulfate
- Food allergies
- Folic acid, iron, selenium, zinc deficiencies
- Gluten sensitive enteropathy
- Vitamin B1, B2, B6, B12 deficiencies

- Systemic Conditions and Factors

- Behcet's disease
- Crohn's disease
- Cyclic and autoimmune neutropenia
- HIV infection/AIDS
- Mouth and genital ulcers with inflamed cartilage syndrome (MAGIC)
- Periodic fever, aphthosis, pharyngitis, adenitis syndrome (PFAPA)
- Reiter's syndrome
- Stress
- Systemic lupus erythematosus

- Genetic/Immunologic

- Localized T-cell dysfunction
- Antibody-dependent cellular cytotoxicity

*Ship JA et al. Quintessence International 2000;31(2):95-112.*

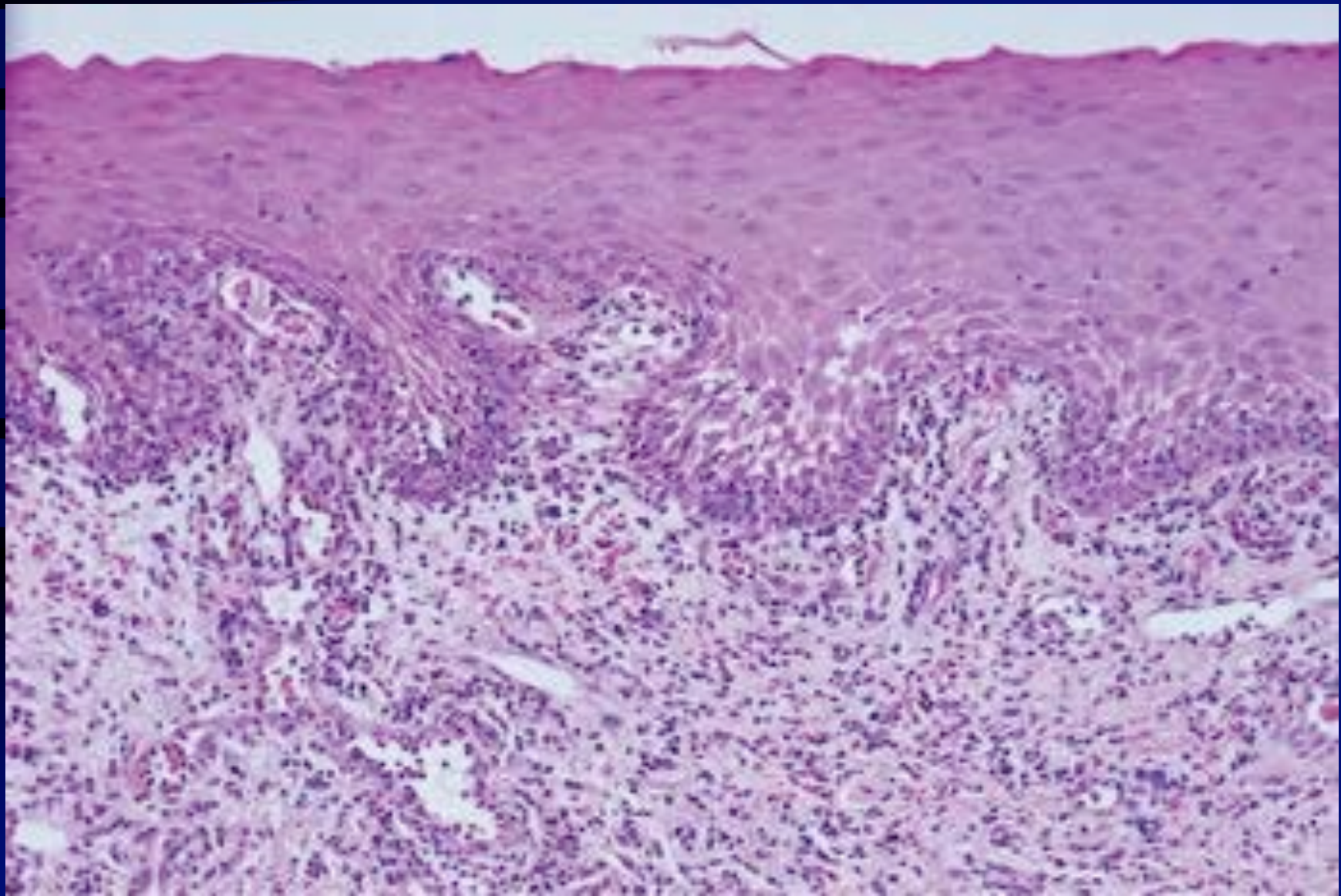
# RAS Earliest Events ?

- Mucosal trauma ?
- Presentation of antigens to mucosal immune cells (eg Langerhans or  $\gamma\delta$  T cells ?)
  - Streptococcal antigens mimicking heat shock proteins ?
  - Viral antigens ?
  - Autoantigens ?
  - Allergens ?
- Triggers a cytotoxic cascade

# Ulcer Formation

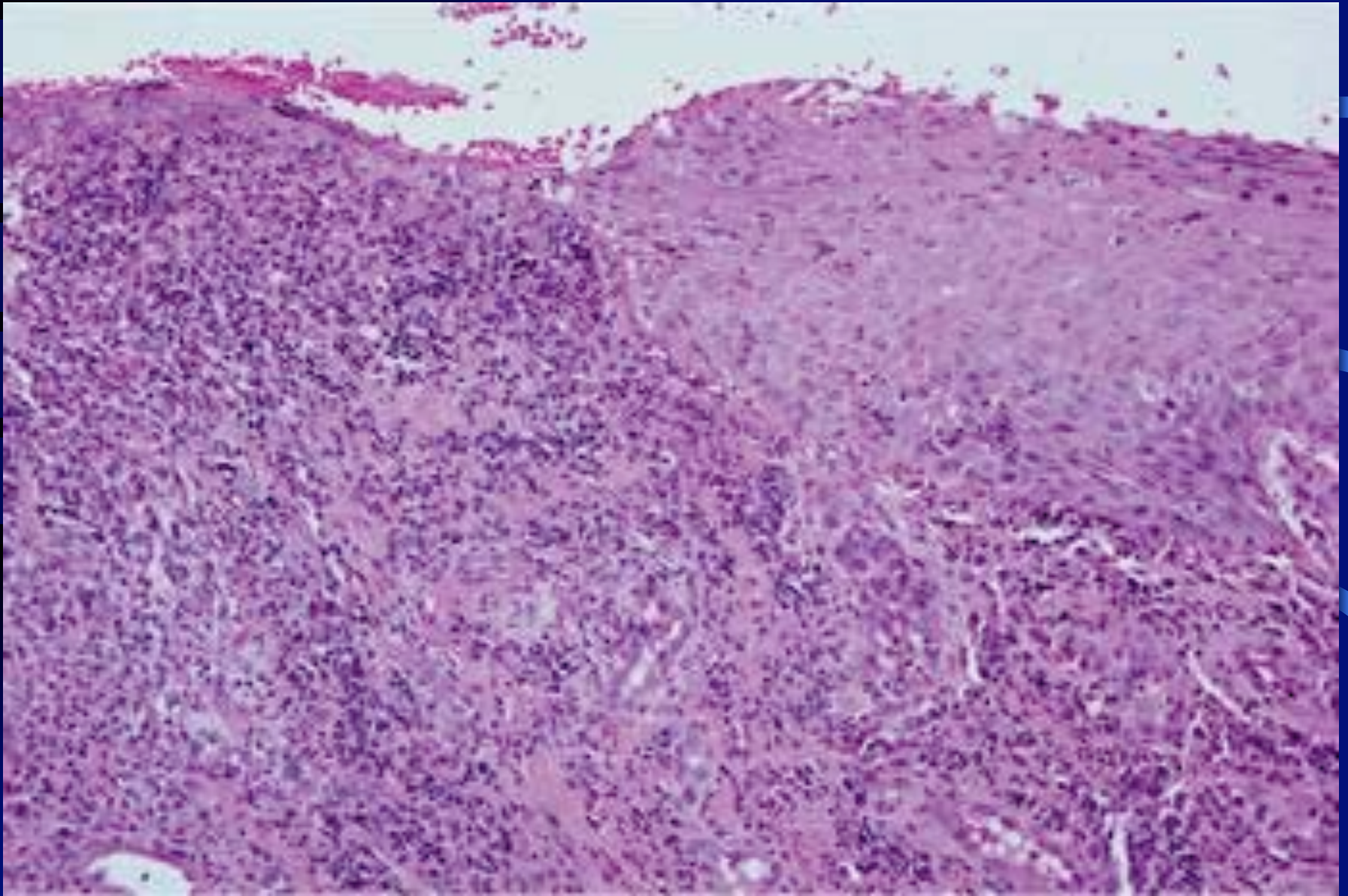
- T-helper cells initially predominate and affect a Th1 immune response
- Adjacent keratinocytes express HLA-DR (MHC-class II) and ICAM-1 molecules
- Local blood vessels express E-selectin and VCAM-1 molecules
- Release of pro-inflammatory cytokines eg IL-1, IL-6, TNF- $\alpha$ , IFN- $\gamma$
- Cytotoxic T-cells mediate keratinolysis
- Neutrophils, macrophages & NK cells also seen

# Histopathology: Pre-ulcerative





# Histopathology: Non-Specific Ulcer



# Why do otherwise healthy people suffer from RAS ?

- Defective immune function ?
  - Gene polymorphisms for IL-1B and IL-6
  - Odds ratio for RAS
    - IL-1B-511 polymorphism (OR 2.5)
    - IL-6-174 polymorphism (OR 2.6)
    - Both IL-1B-511 & IL-6-174 polymorphisms (OR 8.5)

*Bazrafshani MR et al. Genes & Immunity. 2002;3(5):302-5*

## Genotype Associations between RAS patients with High/Low pain

Poly	Genotype	Pain level		OR (95% CI)	$\chi^2$ (p-value)
		Low	High		
IL-1B-511	A/G,A/A	45	28	Ref	6.30 (0.012)
	G/G	9	18	3.21 (1.27-8.14)	
IL-6-174	G/C,C/C	23	13	Ref	2.19 (0.139)
	G/G	31	33	1.88 (0.81-4.36)	

*Thornhill MH et al. OOOOE 2004 (abstract)*

# Diet and RAS

- Equivocal reports
  - Benzoic acid
  - Cinnamaldehyde
  - Nuts
  - Strawberries
  - Chocolate
  - Tomatoes
  - Cheese
- Food intake diaries or elimination diets are difficult to perform
- Patch-testing ?

*Eversole LR et al. OOO. 1982;54(1):33-8.*

*Hay KD et al. OOO. 1984;57:504-7*

*Nolan A et al. J Oral Patthol Med 1991;20:473-5*

# Celiac Disease

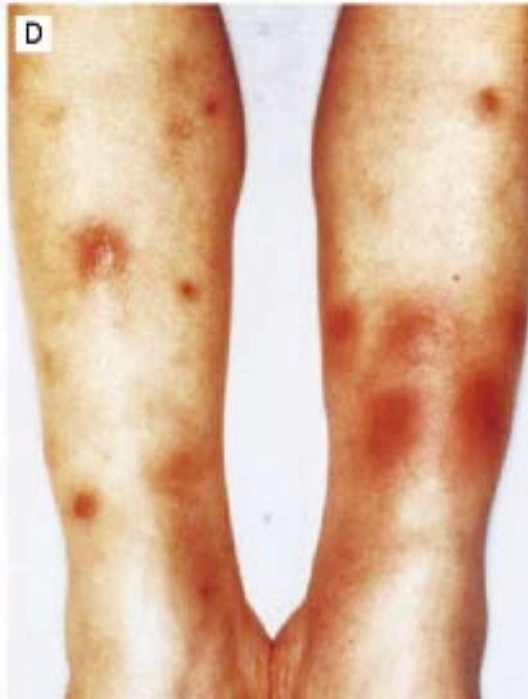
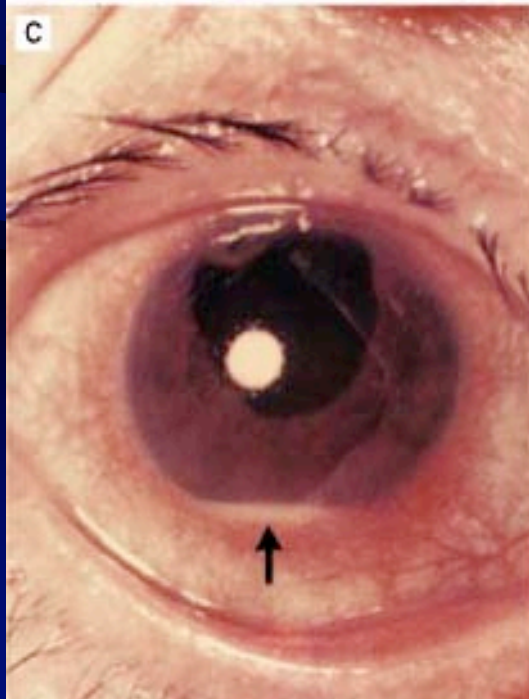
- Celiac sprue or gluten-sensitive enteropathy
- Small intestinal malabsorption
- 4% of patients presenting with RAS
- Gluten-rich foods: cereals eg wheat, rye, barley
- European descent, 7:1 female:male
- Associated clinical findings:
  - chronic diarrhea or flatulence
- Laboratory findings
  - ↑ IgG and IgA antigliadin & IgA anti-endomysial levels
  - Malabsorption tests
- Treatment
  - strict gluten-free diet

# Behçet's Disease

- Recurrent inflammatory disorder of unknown cause: bacterial ?
- Affects Middle Eastern Males & Asian Females
- Onset 3<sup>rd</sup>-4<sup>th</sup> decade
- HLA-B51 association
- Recurrent aphthous ulcers generally precede other signs: genital/skin/eye lesions & others (arthritis, GI lesions, CNS symptoms, vascular lesions)
- Diagnosis based upon criteria: no laboratory tests

*Sakane T et al. NEJM. 1999;341(17):1284-91.*

uveitis



erythema nodosum

FINDING	DEFINITION
Recurrent oral ulceration	Minor aphthous, major aphthous, or herpetiform ulcers observed by the physician or patient, which have recurred at least three times over a 12-month period
Recurrent genital ulceration	Aphthous ulceration or scarring observed by the physician or patient
Eye lesions	Anterior uveitis, posterior uveitis, or cells in the vitreous on slit-lamp examination; or retinal vasculitis detected by an ophthalmologist
Skin lesions	Erythema nodosum observed by the physician or patient, pseudofolliculitis, or papulopustular lesions; or acneiform nodules observed by the physician in a postadolescent patient who is not receiving corticosteroids
Positive pathergy test	Test interpreted as positive by the physician at 24 to 48 hours

\*The criteria were drawn up by the International Study Group for Behçet's Disease.<sup>26</sup> For the diagnosis to be made, a patient must have recurrent oral ulceration plus at least two of the other findings in the absence of other clinical explanations.





Pathergy test: pricking skin with  
sterile needle & waiting 24-48 hours

## Periodic fever, aphthosis, pharyngitis, adenitis syndrome (PFAPA)

- Marshall's syndrome
- Unknown cause: bacterial ?
- Affects young children (mean age <5 yrs)
- Periodicity of episodes q3-4 weeks
- High fevers lasting 4-6 days (up to 40°C)
- Perfect health between episodes

# Reiter's Syndrome

- Reactive arthritis usually following dysentery or a sexually transmitted infection
- HLA-B27-positive
- Oligoarthritis (knee/ankle), conjunctivitis, urethritis, and mouth ulcers most common features

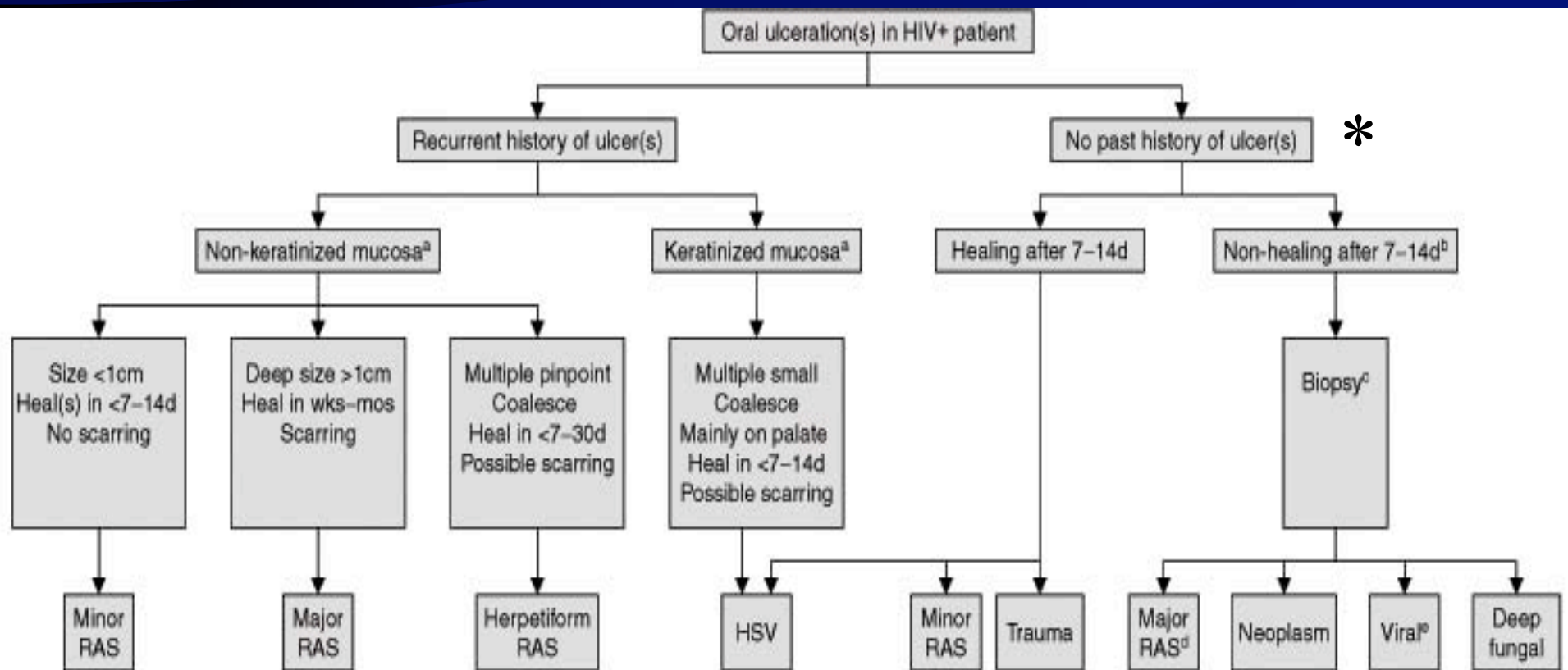
# Hematinic Deficiencies

- Equivocal associations with iron, Vit B1, B2, B6, B12, and folate.
- Blood tests are not recommended routinely in all patients with RAS.
- Indications for blood work:
  - Older patient with recent RAS history
  - Suspicious medical history/review of systems
  - Strict vegetarian patients



# HIV-Associated Aphthous

- CD4 counts  $<100$  cells/mm<sup>3</sup> are predisposed to major RAS
- Other sites may be affected: esophagus, genitals, anus/rectum
- We see this less frequently since HAART
- Diagnosis is important, particularly if no prior history



**Fig. 4.** Diagnosis flow chart for recurrent aphthous stomatitis (RAS) in HIV-infected patients. **a** In some HIV-positive patients (particularly those who have severe immunosuppression), RAS can involve keratinized mucosa, and herpes simplex virus (HSV) infections can involve non-keratinized mucosa; **b** All putative traumatic etiologies have been identified and removed (e.g. sharp teeth or dental prostheses); **c** If neutrophil count is  $<500$  cells/mm<sup>3</sup> consider neutropenic ulceration as a diagnosis, and perform a bacterial culture. Consider potential bleeding problems before biopsy. Analgesics are warranted in the interim, until result of biopsy is known; **d** The histopathologic presentation will be a non-specific ulcer. Empiric therapy with topical corticosteroids is suggested; **e** Culture is warranted to differentiate between HSV and cytomegalovirus.







# Others

- Sweet's Syndrome
  - Acute febrile neutrophilic dermatosis
  - May occur in conjunction with leukemia
- Inflammatory Bowel Diseases
  - Crohn's Disease
  - Ulcerative Colitis
- Medication-induced RAS

# Smoking & RAS

- Cigarette smoking prevents RAS
- Increase keratinization &/or effects of nicotine ?
- Use of smokeless tobacco & nicotine therapy may have a beneficial effect on RAS.

*Bittoun R. Med J Australia 1991;154:471-2*

*Grady D. OOO 1992;74:463-5*

# Steps in managing RAS patients

- History of RAS
- Medical History
  - Medications
  - Review of Systems
- Social History
- Dental History
- Diet/Nutritional History
- Physical Examination
- Laboratory Tests

# History of RAS Outbreaks

- Onset (childhood vs adult)
- Level of pain & quality of life
- Dysphagia
- Weight loss ?
- Recurrence rate
- Healing time
- Possible precipitating factors
- Extra-oral ulcers (eg genitals)
- Prodrome ?
- Associated signs & symptoms during episodes

# Medical History

- Associated medical conditions
- Review of systems
  - Skin, GI, throat, eyes, joints, genitals, neurological system, immune system, hematological
- Medications
  - NSAIDs, nicorandil (UK)

# Social History

- Tobacco history
  - Recrudescence since tobacco cessation ?
- Alcohol

# Oral/Dental History

- Oral hygiene practices/products
- Dry mouth



# Diet/Nutritional History

- Able to eat ?
- Foods
  - Gluten ?
  - Citrus
- Vegetarian ?

# Physical Examination

- Extra-oral
  - Lymphadenopathy ?
  - Skin ?
- Intra-oral
  - Number, location, size

# RAS Treatment Plan:

Treatment dictated by:

- Associated symptoms & ability to function
- Number & location of ulcers
- Recurrence history
- Possible underlying cause

Consider 4 options (can combine):

 No treatment

 Prevention/treatment of/for possible causes

 Topical therapy

 Systemic therapy

 Referral for severe disease

# Infrequent Minor RAS

Treatment to reduce pain

versus

Treatment to reduce healing time

versus

Treatment to prevent recurrences

NB May also consider no treatment

Frequent Minor RAS or Major RAS

Treatment to reduce pain

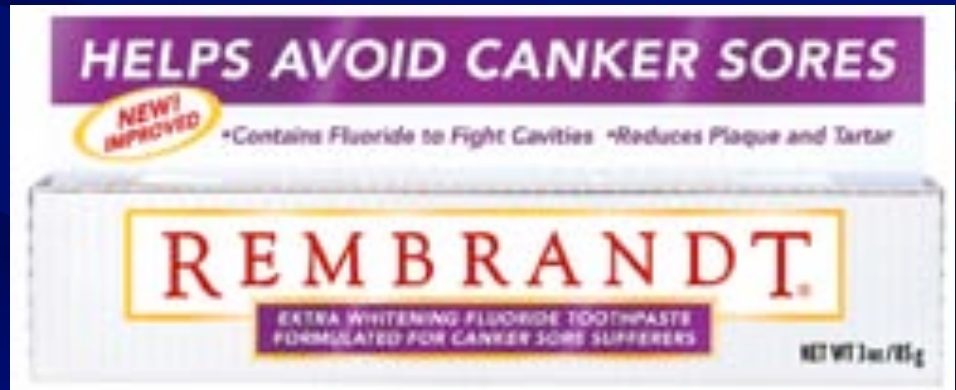
versus

Treatment to reduce healing time

versus

Treatment to prevent recurrences

# Sodium Lauryl Sulfate-Free Toothpastes



# Remove Obvious Possible Causes



- Repair sharp teeth/restorations
- Remove plaque
- Optimize lubrication

# Topical Therapy Categories

- Topical anesthetic agents
- Surface protective agents/bioadhesives
- Anti-inflammatory agents
- Anti-microbials
- Chemical/physical cautery

Over-the-counter (OTC) versus prescription (Rx)



# Evidence-Based Medicine Review & Cochrane Central Register of Controlled Trials Topical Therapies for RAS: 1996-2003

- Penicillin G potassium troches
- 2-octyl-cyanoacrylate
- Thalidomide
- Clobetasol
- Eupatorium laevigatum paste
- Diclofenac delivered in hyaluronan
- Amyloglucosidase and glucose oxidase mouth rinse
- Sodium lauryl sulfate-free dentifrice
- Mometasone furoate lotion
- Medicament containing silicon dioxide, aloe, and allantoin
- Sulfonated phenolics/ sulfuric acid solution
- Amlexanox oral paste
- Low-intensity ultrasound
- Doxymycine-cyanoacrylate
- Mesalazine
- Mouthrinses containing triclosan
- 5 Aminosalicyclic acid

# Clinical Evidence (British Medical Journal)

- **Chlorhexidine:** RCTs found that chlorhexidine gluconate mouth rinses/gels (1%-0.2%) increased the number of ulcer free days and reduced the severity of each episode of ulceration compared with control preparations, but did not affect the incidence of recurrent ulceration. However, similar results were not seen with 0.1% rinse.
- **Topical corticosteroids:** Nine small RCTs found weak evidence that topical corticosteroids may reduce the duration of ulcers and hasten pain relief. No consistent difference in the incidence of new ulcers between topical corticosteroids and control preparations.

*Porter S et al. Clinical Evidence. 2002(7):1232-8.*



# OTC Remedies





# Rx Topical Treatments:

- **Aphthasol** (Amlexanox 5% oral paste)
  - Anti-inflammatory
  - Disp: 5g tube
  - Label: apply over ulcer qid until healed
- **Debacterol** (Sulfonated phenolics; sulfuric acid solution)
  - Chemical cautery
  - Label: one time application for 5-10 seconds



# Rx Topical Treatments:

- Carafate (sucralfate 1g/10ml)
  - Coating agent
  - Disp 14 oz bottle
  - Rinse with 5ml qid and expectorate
  
- Viscous Lidocaine (2%)
  - Topical anesthetic
  - Disp 100ml bottle
  - Rinse with 5ml qid and expectorate



# Rx Topical Treatments:

- Chlorhexidine gluconate 0.12%
  - Antimicrobial
  - May cause staining, dysguesia (bitter)
  - Disp: 16 oz bottle
  - Label: rinse with 15ml bid for 30 secs
- Tetracycline suspension 2.5mg/ml
  - Antimicrobial/anti-inflammatory
  - May cause dysguesia, candidiasis, burning
  - Mix 250mg caplets in 100ml water
  - Label: rinse with 5ml quid and expectorate



# Rx Topical Treatments: Intermediate Potency Corticosteroids

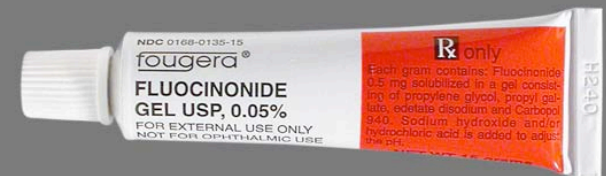
- Kenalog in Orabase  
(triamcinolone acetonide 0.1%)
  - Disp: 5g tube
  - Label: apply a thin film over ulcer after meals and bedtime
  - Do not use for more than 2 weeks





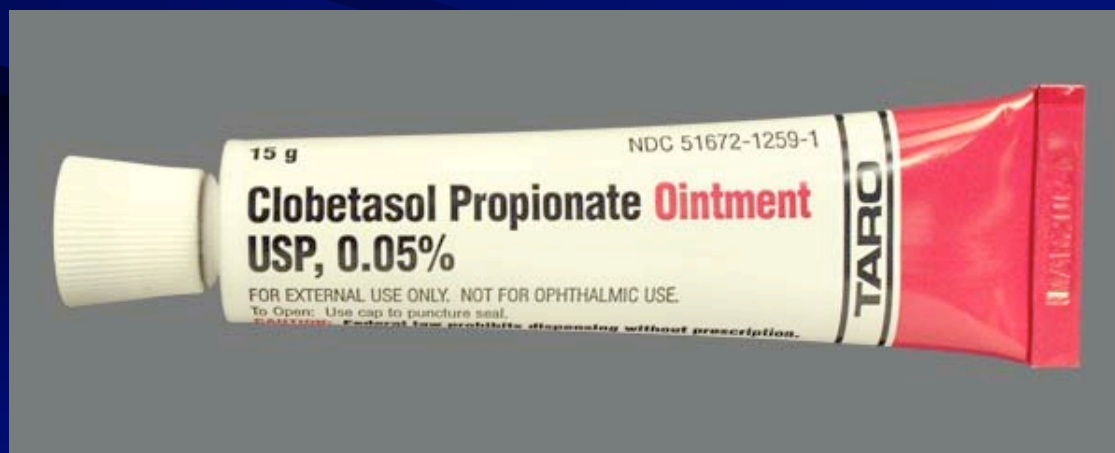
# Rx Topical Treatments: Potent Corticosteroids

- Lidex gel or ointment (fluocinonide 0.05%)
  - Disp: 15g tube
  - Label: apply a thin film over ulcer after meals and bedtime
  - Do not use for more than 2 weeks
  
- Decadron Elixir (dexamethasone 0.5mg/5ml)
  - Indicated for multiple or difficult to reach lesions
  - Disp: 100ml
  - Label: rinse with 5 ml for 5 minutes qid and expectorate
  - Do not use for more than 2 weeks



# Rx Topical Treatments: Ultra-Potent Corticosteroids

- Temovate ointment (clobetasol 0.05%)
  - Disp: 15g tube
  - Label: apply a thin film over ulcer bid
  - Do not use for more than 2 weeks



# Problems with Topical Treatments

- Drug is easily washed away or rubbed off
- Topical anesthetics have a short-lived effect
- Often difficult to apply due to location
- Cost may be a disincentive to buy OTC/Rx

# Systemic Medications

- Intralesional steroid injections
  - Triamcinolone, dexamethasone, betamethasone
- Systemic steroids +/- azathioprine
- Pentoxifylline
- Cochicine
- Thalidomide
- Dapsone
- Levamisole
- Tetracycline/Niacinamide
- Anti-TNF agents ? (etanercept, infliximab)

NB All systemic medications have potential side-effects and interactions, and must be used by trained specialists.

# Prednisone



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- Glucocorticoid & immunosuppressant
- Decreases inflammation by suppressing chemotaxis of polymorphonuclear neutrophil leukocytes, reduces capillary permeability lymphocytic activity.
- Used to gain initial control of severe disease
- Dose: initially give 0.5-1.0 mg/kg a day for 1 to 2 weeks and monitor the patient's response
- If there is no response, dosage should be increased in 0.25 mg/kg increments a day until the lesions respond, complications arise, or a maximum dose of 2.0 to 2.5 mg/kg is reached
- Multiple adverse effects with long-term use

# Pentoxifylline

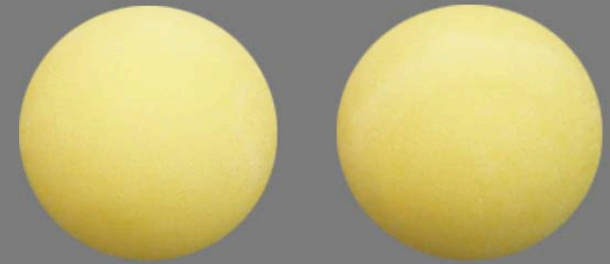


- Methylxanthine derivative
- Primarily used for peripheral vascular disease by increased erythrocyte flexibility and decreased blood viscosity.
- May also modulate effects of TNF- $\alpha$
- Dose: 400mg tid after meals for 4 weeks
- Few side-effects (after 6 months)
- Open-label studies suggest long-term reduction in recurrence rate

*Wabba-Yahav. J Am Acad Dermatol 1995;33:680-2*

*Pizarro A et al. Br J Dermatol 1995;133: 659-60*

# Colchicine



- Anti-inflammatory agent
- Inhibits the migration of neutrophils into the area of inflammation.
- Toxic effects of colchicine are related to its antimitotic activity within proliferating tissues such as the skin, hair, and bone marrow.
- Dose: 0.5mg tid for up to 8 weeks or longer
- Adverse GI effects occur in as many as 80% of patients
- Likely little effect on recurrence rate following discontinuation

*Ruah CB et al. Arch Otolaryngol Head Neck Surg 1988;114:671-5*

*Katz J et al. J Am Acad Dermatol 1994;31:459-61*

# Thalidomide



- Immunomodulator
- Decreases the production of TNF $\alpha$  and inhibit leukocyte chemotaxis.
- **Teratogenic (need STEP)**
- In HIV + study populations adverse effects were fatigue, rash and peripheral neuropathy.
- Dose: 200mg/day for 4 weeks
- Not recommended for maintenance therapy

*Jacobson JM et al. NEJM 1997;336(21):1487-93.*



# Oral Herpes

- Primary Infection
  - Primary Herpetic Gingivostomatitis
- Secondary Infection
  - Herpes Labialis
  - Intra-Oral Herpes

# Herpes Virus Family

- Herpes simplex type 1 and 2
- HHV3 - Cytomegalovirus
- HHV4 - Epstein-Barr virus
- HHV5 - Varicella zoster virus
- Human herpes type 6
- Human herpes type 7
- Kaposi's associated herpes virus (type 8)

# Latency

- Herpes simplex type 1 and 2 - sensory ganglia
- Cytomegalovirus - bone marrow cells
- Varicella zoster virus - sensory ganglia
- Epstein-Barr virus - lymphocytes
- Human herpes type 6 - lymphocytes
- Human herpes type 7 - lymphocytes
- Kaposi's associated herpes virus (type 8) - endothelial cells

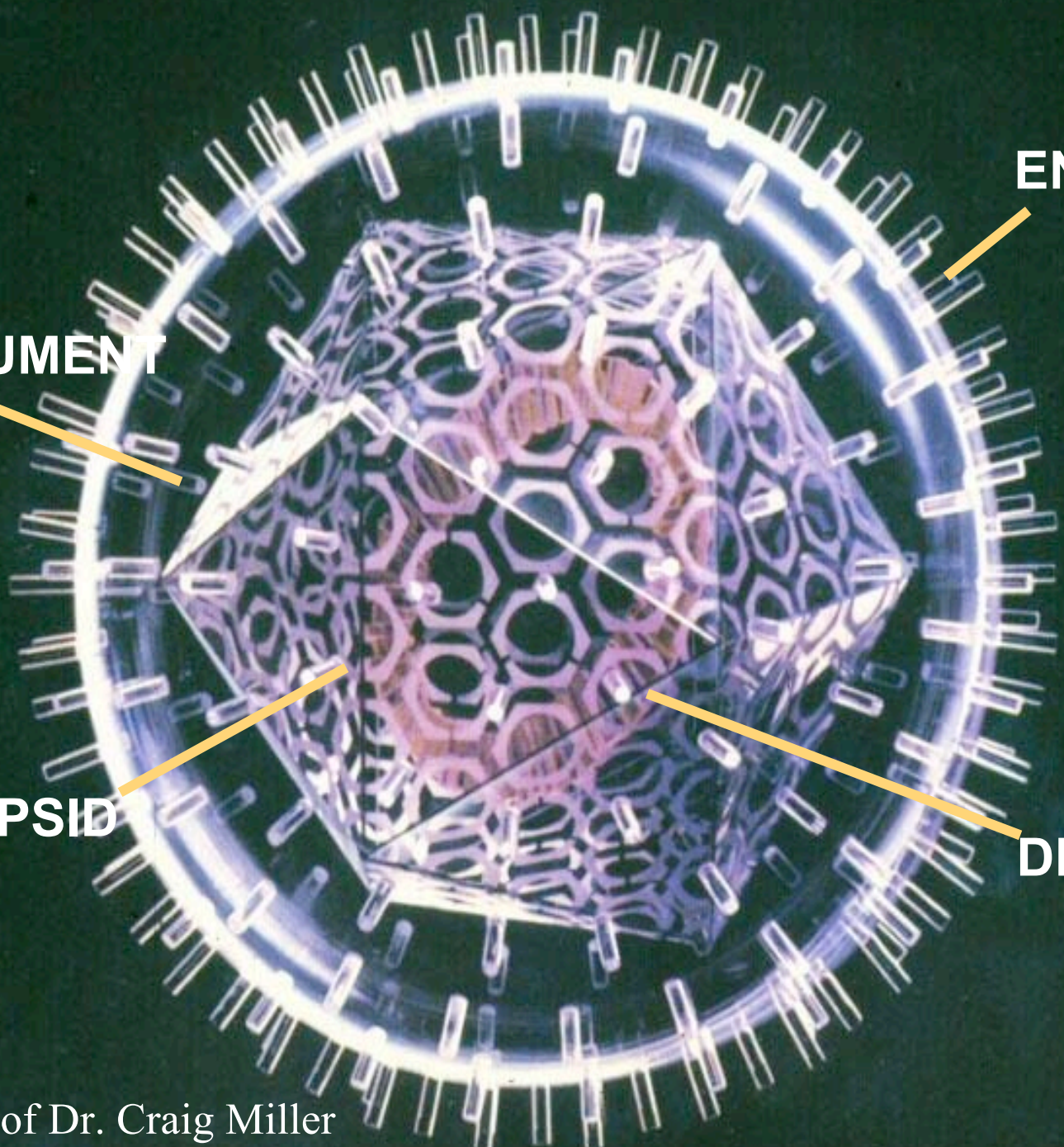
**TEGUMENT**

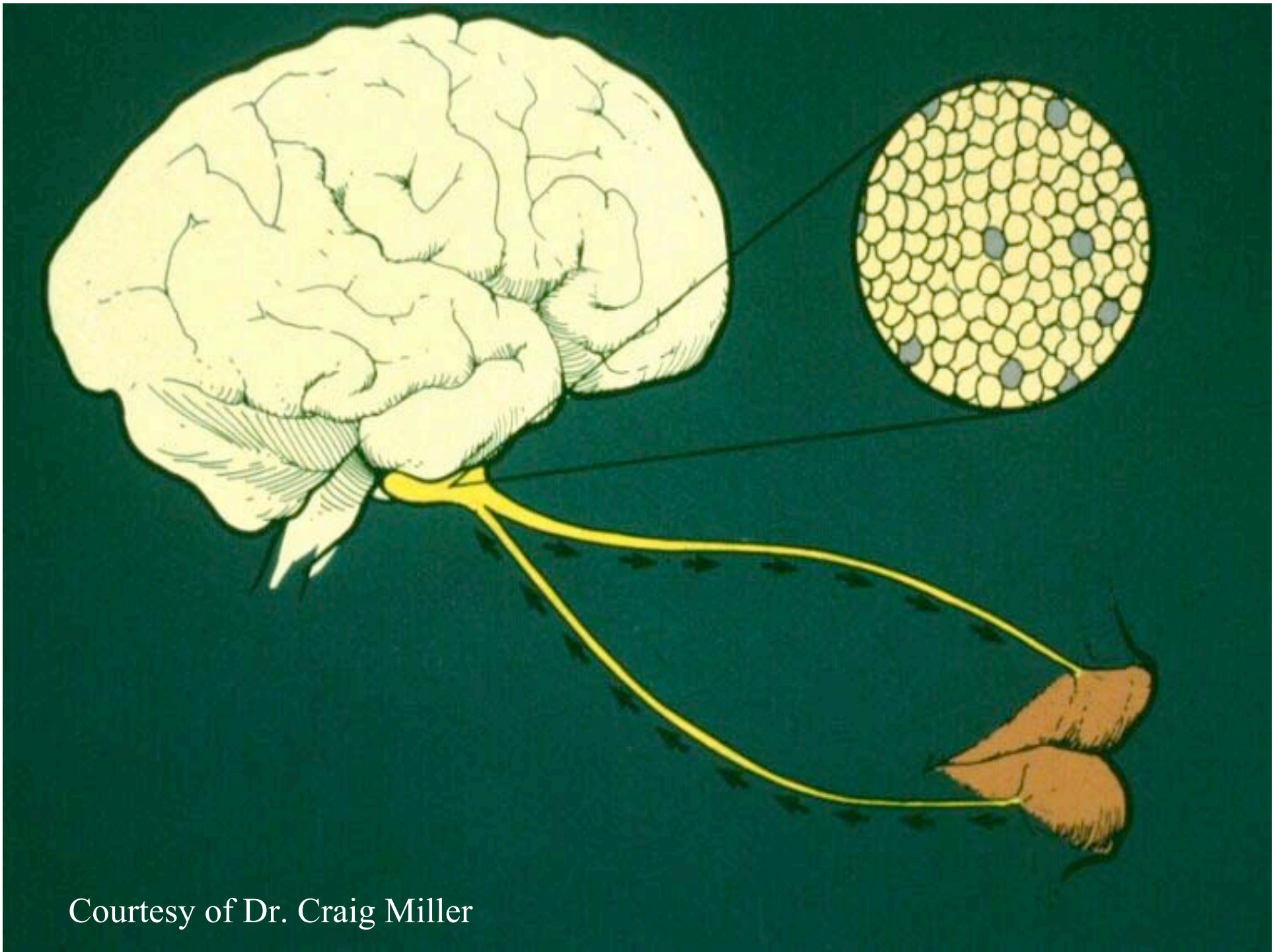
**ENVELOPE**

**CAPSID**

**DNA CORE**

Courtesy of Dr. Craig Miller





Courtesy of Dr. Craig Miller



Chemicals



Electricity



Radiation



Trauma



Sun Light

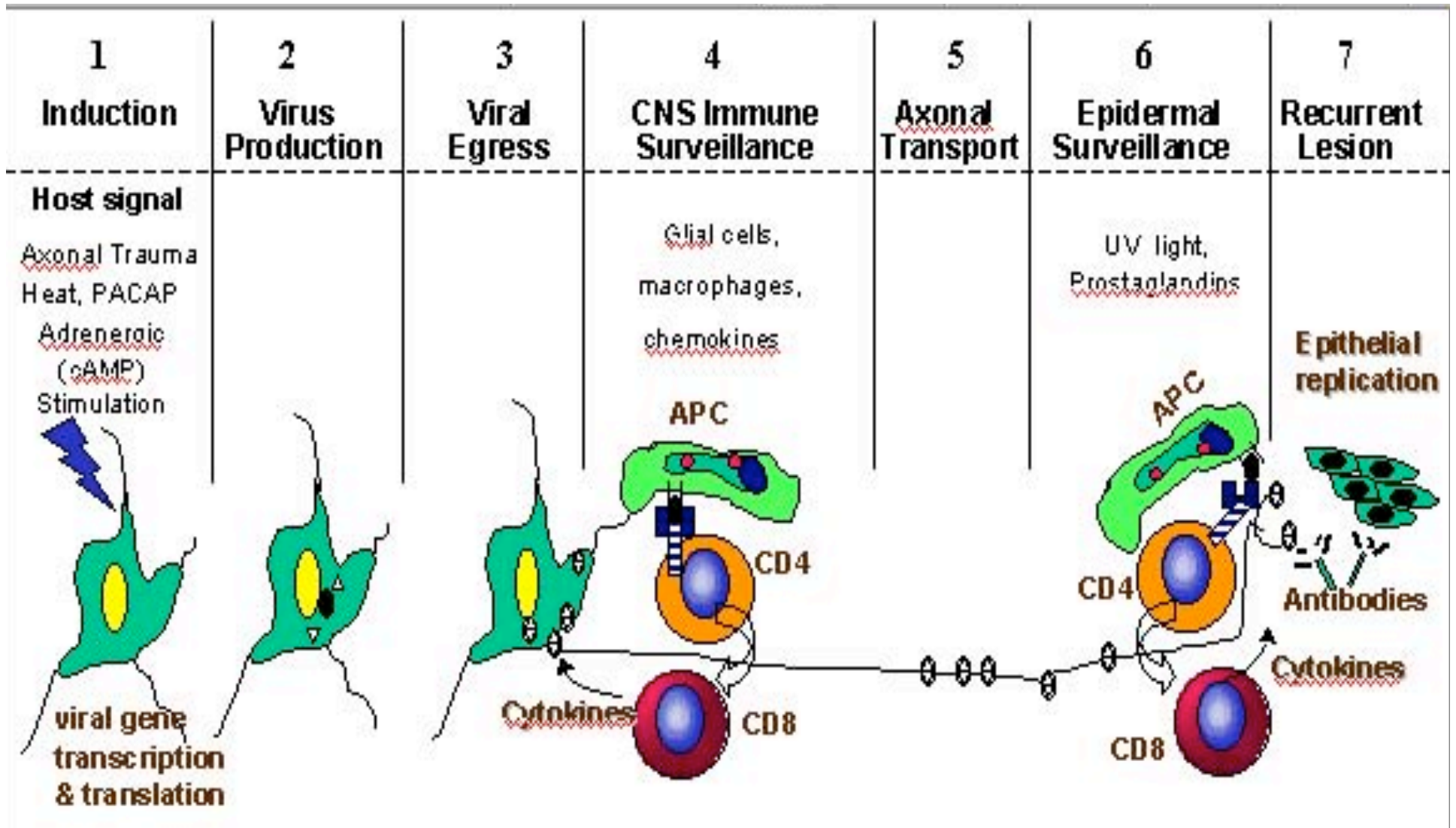


**(re) Activation**



Wind

Courtesy of Dr. Craig Miller



24  
hr



48 hr



72 hr

*Asymptomatic shedding*

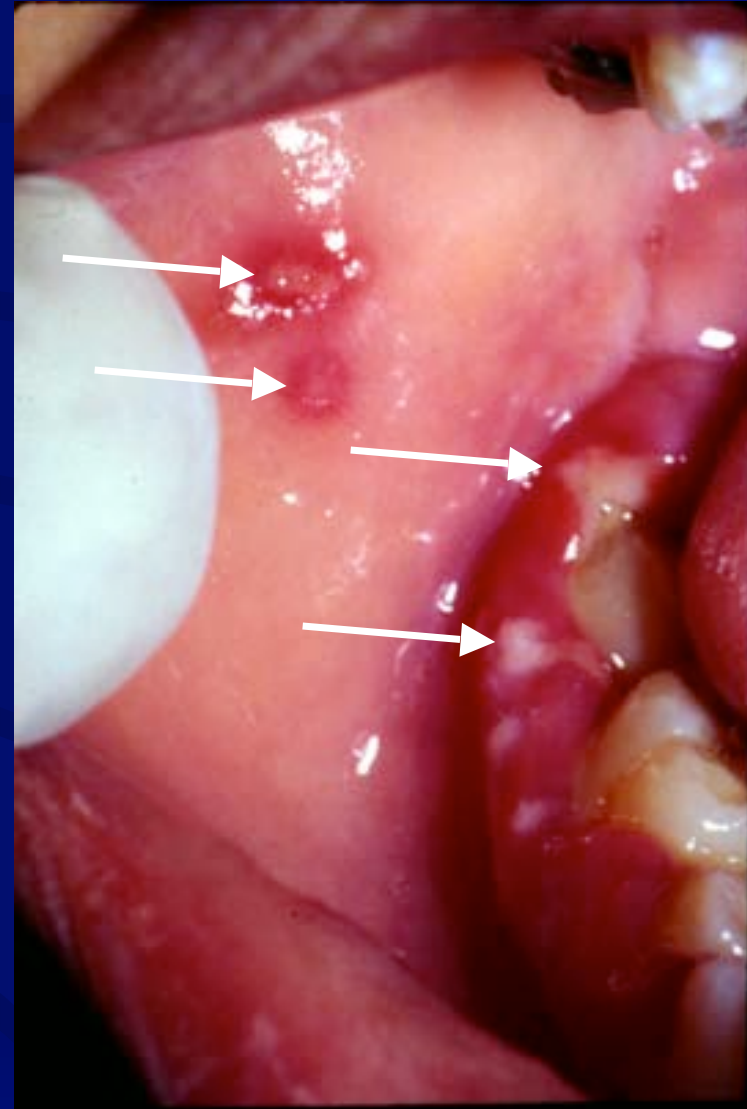
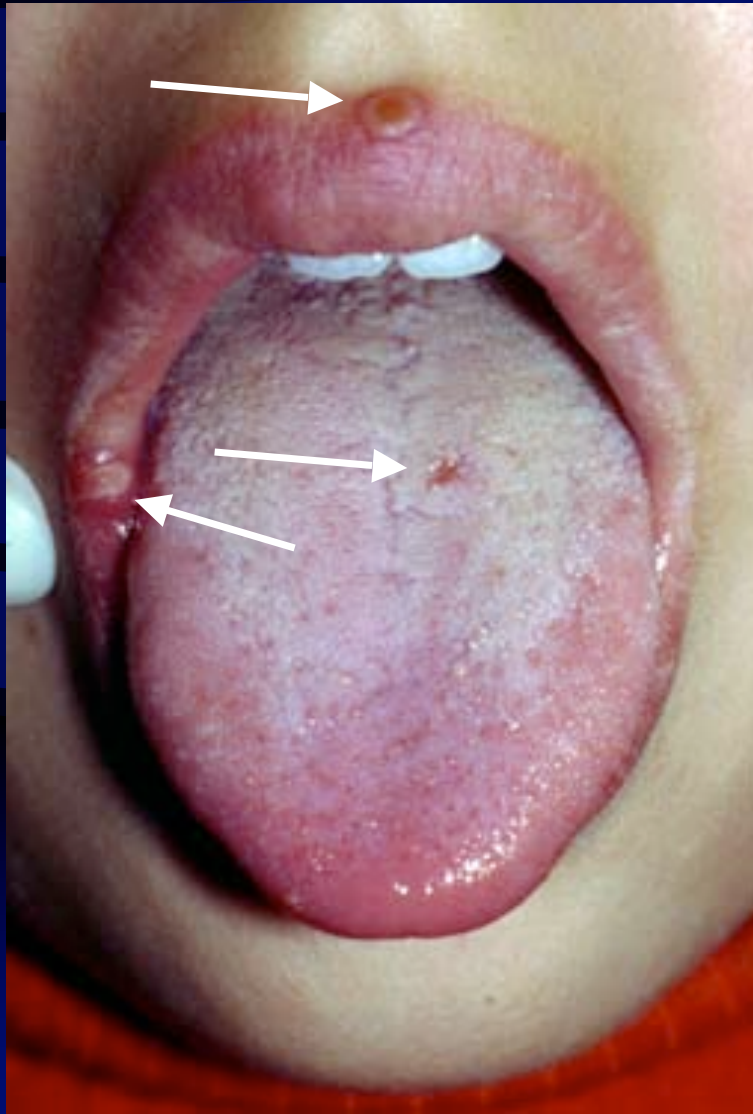
Courtesy of Dr. Craig Miller

# HSV 1

- Seropositivity to HSV 1
  - 40% in under 20 age group
  - 65% in over 70 age group
- Shedding
  - Asymptomatic shedding can occur in HSV seropositive patients
  - Especially following surgical procedures
  - Especially in immunocompromised patients



# Primary Herpetic Gingivostomatitis



# Primary Herpetic Gingivostomatitis

## Treatment Decisions:

- Do you treat with intent to cure ?
- Do you treat to palliate a condition which would resolve on it's own ?
- Do you treat to reduce or prevent the chances for recurrence ?
- Do you counsel patients about risks of contagion ?

# Primary Herpetic Gingivostomatitis

## Treatment Options:

- **Doing nothing**
- **Doing something reversible**
  - Patient-oriented instructions
  - Medication
    - Over-the-counter
    - Prescription
      - Topical
      - Systemic
- **Doing something irreversible**

# Primary Herpetic Gingivostomatitis

## Supportive/Palliative Treatment Plan:

- Treatment dictated by severity of infection
- Patient Instructions: (give to parent)
  - Forced fluids
  - Maintain nutrition (supplements if necessary: Pediasure/Ensure)
  - Rest
  - Avoid touching lesions and then eyes, genitals etc
  - Possible referral to MD if infant not drinking because of pain
- Medications:
  - Topical anesthetic solutions (OTC vs Rx)
  - Mucosal coating agents (OTC)
  - Analgesics (OTC vs Rx)
  - Antiviral agents (Rx)

# Primary Herpetic Gingivostomatitis

## Medications 1:

### **OTC Topical Anesthetic/Mucosal Coating Agent**

**Diphenhydramine elixir (Children's Benadryl)**

**12.5mg/ml** (may mix with kapectate or Maalox 50% by volume)

Disp: 4oz bottle

Label: rinse with 5ml for 2 minutes every 2 hours and spit out.

### **Rx Topical Anesthetic**

**Lidocaine 2% viscous solution\*\***

Disp: 100ml bottle

Label: rinse with 10 ml for 2 minutes and spit out.

\*\* may diminish gag reflex, better suited for older patients

# Primary Herpetic Gingivostomatitis

## Medications 2:

### **OTC Analgesic**

**Acetaminophen or ibuprofen suspension/tablets as directed for body weight**

### **Rx Antivirals\*\*\***

**Acyclovir suspension/tablets 200mg as directed for body weight**

**\*\*\* Generally only indicated for immunocompromised patients, but may be prescribed if instituted very early on**

# Secondary Herpes Infections

## Etiology/Diagnosis

- Reactivation of the latent HSV in the sensory ganglion of the trigeminal nerve.
- **Precipitating factors:** fever, stress, sunlight, trauma, hormonal swings.
- **Herpes labialis:** clusters of vesicles on lips which rupture within hours then crust. **Esthetically obtrusive.**
- **Intraoral herpes:** single or small clusters of vesicles forming on keratinized tissue of hard palate & gingivae, which quickly rupture forming **painful ulcers**

# Recurrent Herpes Labialis

- The prevalence ranges from 15-45%
- Usually 1 to 6 outbreaks a year.
- Approx 50-60 % of patients experience prodromal symptoms



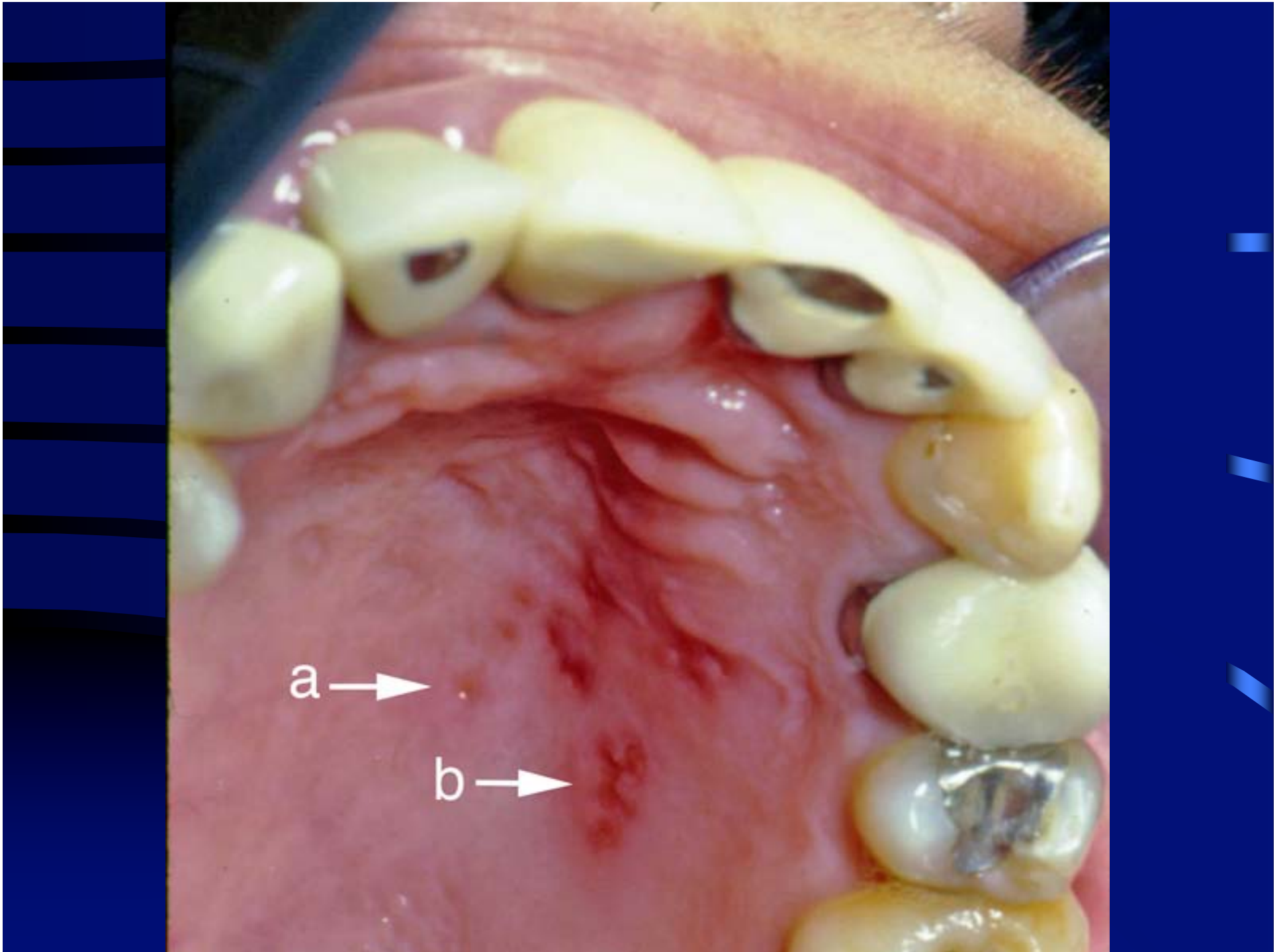
# Recurrent Herpes Labialis (HSV-1)

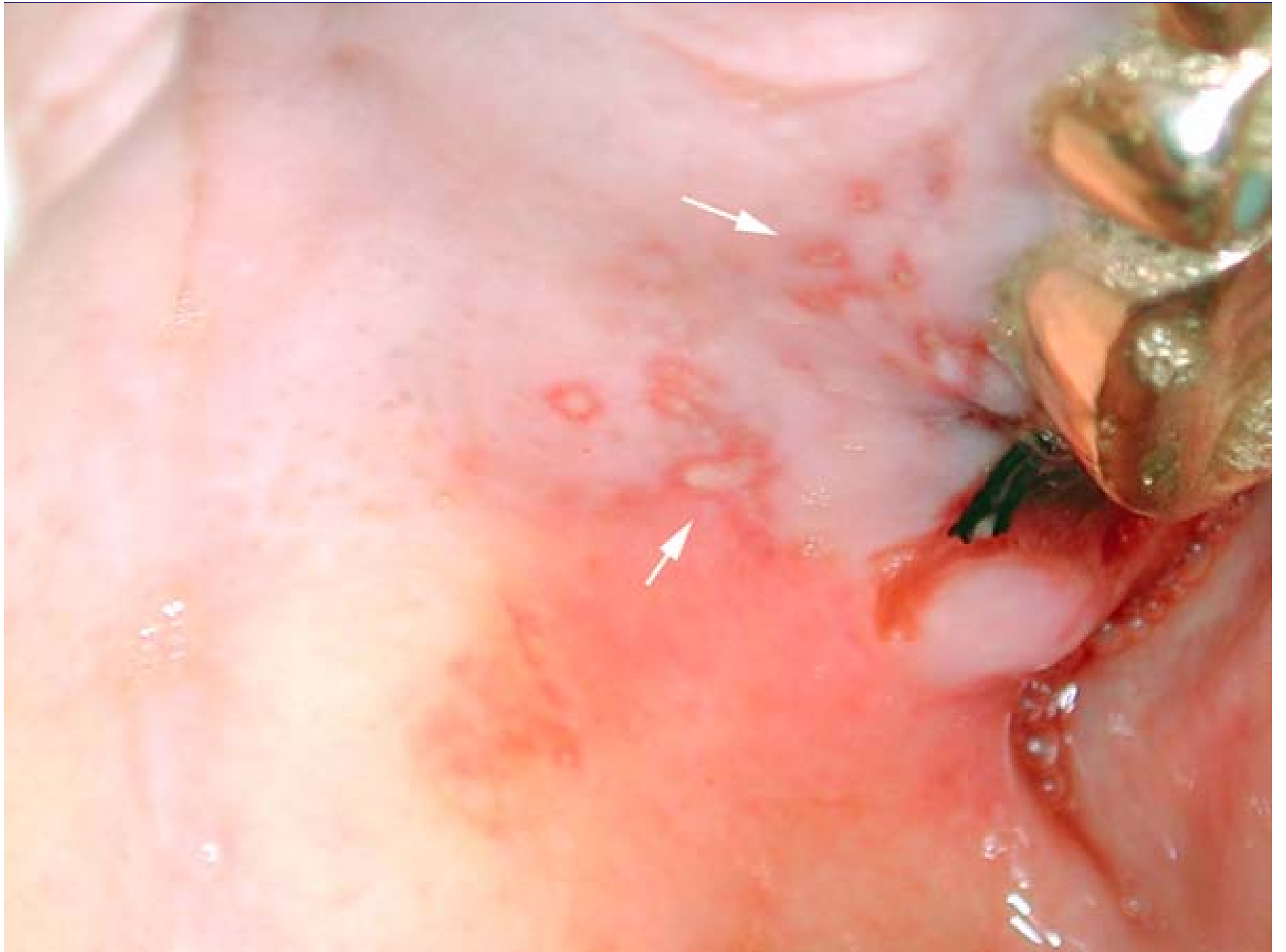




# Secondary Intra-Oral Herpes







# Secondary Recurrent Herpes Labialis Treatment

- Topical
  - OTC
  - Prescription
- Systemic
  - OTC
  - Prescription

# Secondary Recurrent Herpes Labialis

## Topical treatments

- Topical
  - Ice
  - L-lysine
  - Bioflavonoids
  - Evaporants-Dessicants
    - Viroxyn, Ether
  - Emollients
    - Zilactin, Carmax, Herpecin, Blistex, ChapStick



# New technologies

- Hydrocolloid patch
- Not yet in US marketplace





## These Foods (100 gram portions) Contain a Surplus of:

### Lysine/Arginine

Milk	0.3/0/1
Fish	1.8/1.2
Chicken	1.8/1.3
Beef	1.6/1.2
Pork	1.3/1.0
Brewers yeast	3.3/2.2
Soybean/Legumes	1.7/1.4

### Arginine/Lysine

Nuts	2.7/0.6
Chocolate	0.7/0.6
Popcorn	1.2/0.8
Jello/gelatin	7.9/4.2
Brown rice	0.4/0.3
Raisins/seeds	4.0/1.4
Whole wheat bread	0.6/0.3

# Secondary Recurrent Herpes Labialis

## Topical antivirals initiated early in course

- FDA approved Topical therapy  
*Shortens healing by <1 day*

Rx: Penciclovir cream 1%  
(Denavir)

Disp: 2g tube

Label: dab on lesion every 2  
hours for 4 days

Rx: Docosanal cream (Abreva)  
OTC

Disp: 2g tube

Label: dab on lesion five times  
per day for 4 days



**Spruance et al. 2003 ([n=1385] 0.5 days shorter; duration pain shorter 0.35 days)**



# Secondary Recurrent Herpes Labialis

Systemic antivirals initiated early in course

- FDA approved systemic therapy

Rx: Valacyclovir 1g tablets (Valtrex)

Disp: 4 tabs

Label: 2 tabs PO every 12 hours for 2 doses



# Secondary Recurrent Herpes Labialis

## Prophylactic antiviral treatment to reduce recurrences

- No clinical trials have been published for herpes labialis, although anecdotal success reported
- Valacyclovir 500mg-1g qd
- Minimal side-effects from long term use (>1yr)

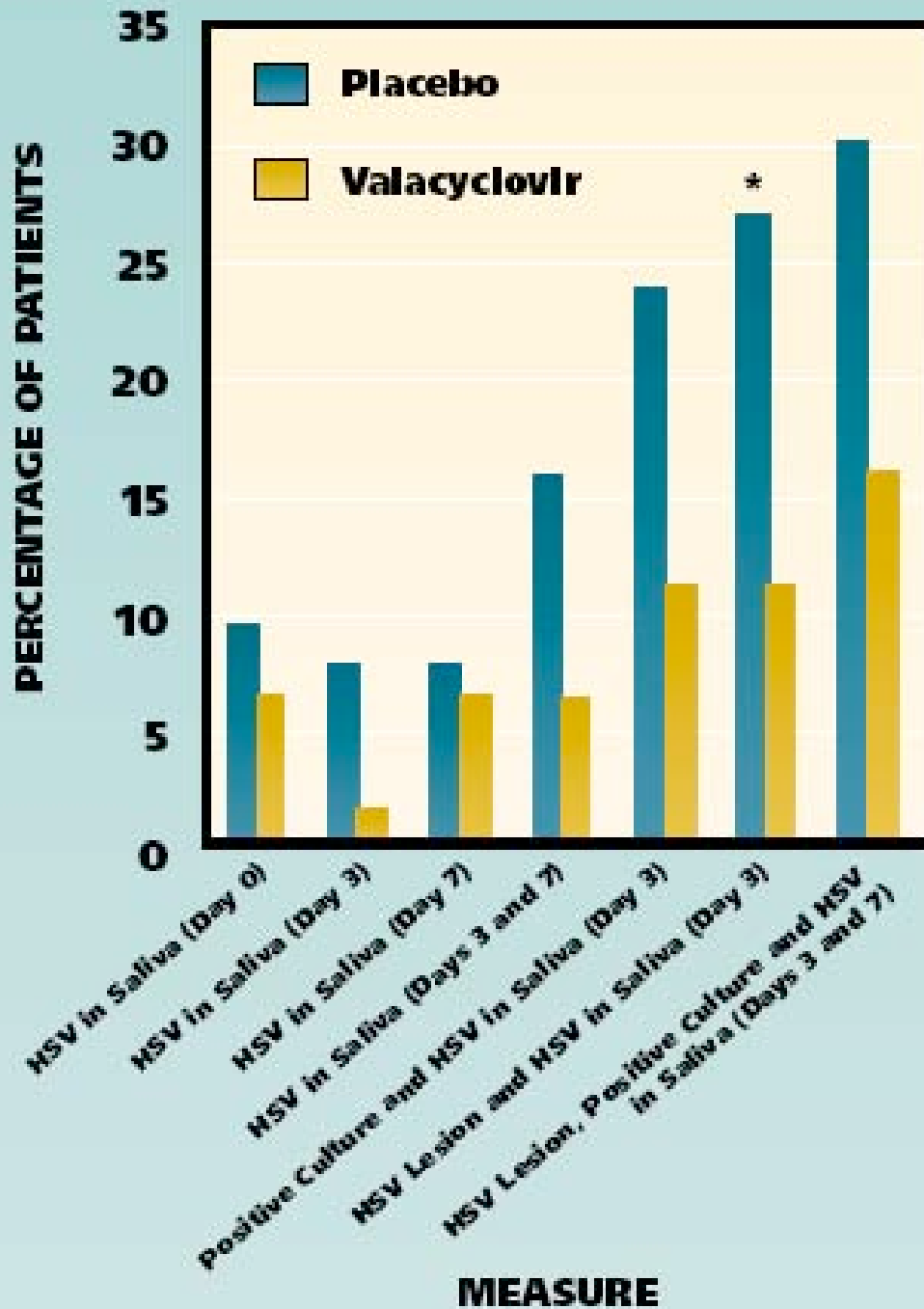
## 2-Day Course Valacyclovir as a Prophylactic for Suppression of Dentally Induced RHSV

- Prospective, randomized, double-blind, placebo-controlled study was performed (n=125)

2g taken 1 hr before dental tx

2g taken same evening

1g taken bid the next day



## Valtrex (Valacyclovir) only FDA approved drug for the prevention of oral herpes simplex virus recurrences (2002)

Data from this clinical trial suggest 20% of HSV-1 seropositive patients develop clinical HSV lesions and 30% develop clinical signs of HSV infection within 1 week following dental treatment. Valacyclovir was found to significantly reduce viral recrudescence and shorten the duration of symptoms of oral RHSL following dental treatment.

## CDC Recommended Regimens for treatment of Primary Episode of Genital Herpes

- Acyclovir 400 mg orally tid for 7-10 days, or
- Acyclovir 200 mg orally 5 x d for 7-10 days, or
- Famciclovir 250 mg orally tid for 7-10 days, or
- Valacyclovir 1 g orally bid for 7-10 days



CDC: 1998 Guidelines for Treatment of Sexually Transmitted Diseases. *MMWR* 47:1-118, 1998.



## **CDC Recommended Regimens for Treatment of Recurrent Herpes Infection**

- **Acyclovir 400 mg orally tid for 5 days, or**
- **Acyclovir 200 mg orally 5 x d for 5 days, or**
- **Acyclovir 800 mg orally bid for 5 days, or**
- **Famciclovir 125 mg orally bid for 5 days,**
- **Valacyclovir 500 mg orally bid for 5 days.**

CDC: 1998 Guidelines for Treatment of Sexually Transmitted Diseases. *MMWR* 47:1-118, 1998.

## CDC Recommended Regimens for Daily Suppressive Therapy of Recurrent Herpes Infection

- Acyclovir 400 mg bid, or
- Famciclovir 250 mg orally bid, or
- Valacyclovir 250 mg orally bid, or
- Valacyclovir 500\* mg or 1,000<sup>¶</sup> mg orally qd

**Baker D & Eisen D. Cutis 71:239,2003. 4 month preventive study: 28/49 (60%) \*Valacyclovir recurrence-free vs. 18/49 (38%) placebo**

<sup>¶</sup>The higher dose may be required for patients who have more frequent (>10) recurrences per year.

## Management of recurrent oral herpes simplex infections

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and London, UK

HARVARD SCHOOL OF DENTAL MEDICINE AND KING'S COLLEGE LONDON DENTAL INSTITUTE  
AT GUY'S

The literature has been reviewed for evidence of the efficacy of antiviral agents in both the prophylaxis and treatment of recurrent oral herpes simplex virus (HSV) infections and discussed by a panel of experts. Emphasis was given to randomized controlled trials. Management of herpes-associated erythema multiforme and Bell palsy were also considered. The evidence suggests that 5% acyclovir (ACV) in the cream base may reduce the duration of lesions if applied early. Recurrent herpes labialis (RHL) and recurrent intraoral HSV infections can be effectively treated with systemic ACV 400 mg 3 times a day or systemic valacyclovir 500 to 1000 mg twice a day for 3 to 5 days (longer in the immunocompromised). RHL in the immunocompetent can be effectively *prevented* with (1) sunscreen alone (SPF 15 or above), (2) systemic ACV 400 mg 2 to 3 times a day, or (3) systemic valacyclovir 500 to 2000 mg twice a day. Valacyclovir 500 mg twice a day is also effective in suppressing erythema multiforme triggered by HSV. Further studies are needed to compare treatment efficacy between topical penciclovir, docosanol, and ACV cream for RHL. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103(suppl 1):S12.e1-S12.e18)

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## WWOM IV: Evidence-based treatment of RHL in the immunocompetent host

- (1) 1% penciclovir cream applied every 2 hours from the time of prodrome until lesions are healed.
- (2) 10% docosanol cream applied every 2 hours from the time of prodrome until lesions are healed.
- (3) 5% ACV cream applied every 2 hours from the time of prodrome until lesions are healed.
- (4) 400 mg of systemic (oral) ACV 3 times a day for 5 to 7 days; it is unclear if 800 mg twice a day would also be efficacious.
- (5) 500 to 2000 mg of valacyclovir twice a day for 1 day or 500 mg of famciclovir 2 to 3 times a day for 3 days are also effective in aborting lesions.

## WWOM IV: Evidence-based prophylaxis of RHL in the immunocompetent host

- (1) Sunscreen alone (SPF 15 or above).
- (2) Systemic (oral) ACV 400 mg 2 to 3 times a day.
- (3) Systemic (oral) valacyclovir 500 to 2000 mg twice a day.

The duration of prophylaxis would depend on trigger factors such as UV exposure or dental treatment.

## WWOM IV: Evidence-based treatment of recrudescient HSV infections in the immunocompromised host

- (1) Systemic (oral) ACV 400 mg 3 times a day for 10 days or longer (often up to several weeks).
- (2) Systemic (oral) valacyclovir 500-1000 mg twice a day for 10 days or longer (often up to several weeks).
- (3) Famciclovir has been recommended as an alternative at 500mg 2 times a day by the Centers for Disease Control and Prevention for up to 1 year.

## WWOM IV: Evidence-based prophylaxis of recrudescence of HSV infections in the immunocompromised host

- (1) Systemic (oral) ACV 400-800 mg 3 times a day.
- (2) Systemic (oral) valacyclovir 500-1000 mg twice a day.
- (3) Systemic (oral) famciclovir 500-1000 mg twice a day.

# Varicella Zoster Virus Infection

- Primary VZV:  
Chicken pox
- Secondary VZV:  
“Shingles”
  - May affect oral cavity/face if it reactivates along distribution of V1/2/3

