ORAL MEDICINE & PATHOLOGY IN 2105: *What’s Hot & What’s Not*

Iowa Dental Association
Annual Session
Iowa Events Center
Des Moines, IA
May 1, 2015

Denis P. Lynch, D.D.S., Ph.D.
denis.lynch@marquette.edu

Outline
- Immunologically-mediated diseases
  - Recurrent aphthous ulcers
  - Lichen planus
  - Mucous membrane pemphigoid
- Infectious diseases
  - Human herpes virus, Type I
  - Oral candidiasis

Synopsis
- Major clinical signs and symptoms
- Diagnostic criteria and tests
- Currently accepted therapeutic modalities

Outline
- Oral cancer
- Xerostomia

References

**COLOR ATLAS OF COMMON ORAL DISEASES**

- Bryan E. O'Neal
- Robert P. Langlais
- Craig S. Miller
- J.R.U. NeilGarrow
Aphthous Ulcers

Etiology and Epidemiology
- Immune dysfunction
- Microbial cross-reactivity
- Nutritional deficiency
- Hormonal imbalance
- “Stress”
- Most common oral ulcer
  - 50% of adults in USA affected

Clinical Features
- Never preceded by vesicles
- Only affect non-keratinized mucosa
  - NOT hard palate
  - NOT attached gingiva
- Multiple clinical forms

Minor Aphthous Ulcers
- Most common form
- Small (<1.0 cm)
- Shallow ulcer
- Pseudomembranous covering
- Erythematous halo
- Persist for 7 – 10 days
- Heal without scarring

Major Aphthous Ulcers
- More severe form
- Larger (>1.0 cm)
- Deeper (into muscle)
- Persist for 2-6 weeks
- Heal with scarring
Herpetiform Aphthous Ulcers
- NOT due to infectious agent
- Cluster of multiple small aphthae
- Extremely painful
- Soft palate
- Alveolar mucosa

Behçet’s Syndrome
- Oral ulcers
- Ocular ulcers
- Genital ulcers

Differential Diagnosis
- Other viral infections
- Traumatic ulcers
- Pemphigus vulgaris
- Cicatricial pemphigoid
- Crohn’s disease
- Other systemic disease

Diagnosis
- History
- Clinical signs and symptoms
- Biopsy ONLY to rule out other entities

Treatment
- OTC medications
- Immunosuppressives
- Occlusive dressings
- Chemical cautery
- Ablation
- Topical antimicrobials
- Thalidomide

Occlusion
### Sodium Lauryl Sulfate
- Extracted from palm oil and coconut oil
- Anionic surfactant (detergent)
  - Makes toothpastes “foamy”
- At higher concentrations, also an effective biocide, pesticide and shark repellent (!)
- Decreases effectiveness of topical F^-  
- Triggers oral aphthae in some patients

### Cortisone
- Described in 1935
- Converted to hydrocortisone in the liver (active form)
Topical Corticosteroid Potency

- Class I (superpotent) – clobetasol
- Class II (high potency) – fluocinonide
- Class V (moderate potency) – triamcinolone
- Class VII (low potency) – hydrocortisone

Kenalog in Orabase

- Only FDA-approved topical corticosteroid for oral mucosal use
- Least potent topical corticosteroid used in dentistry

Why only Kenalog?

- Animal testing
- Investigational New Drug (IND) application
- Clinical Trials
  - Phase 1 – drug safety; <100 healthy volunteers
  - Phase 2 – drug dose; hundreds of volunteers with disease
  - Phase 3 – safety and efficacy; thousands of volunteers; placebo or current competitive drug comparison

Why only Kenalog?

- New Drug Application (NDA)
  - Official labelling approved
  - Known side effects and warnings
  - Diseases/conditions or which drug can be used
  - Postmarketing monitoring
    - New side effects
    - Safety updates

Why only Kenalog?

- Time frame of 8-10 years
- Cost of 500 million - 2 billion dollars
- 20% chance of any new drug going from IND application to market

High/Super Potency Topical Corticosteroids
Swish and Spit
Swish and Swallow

Injectable Kenalog

- Good for solitary major aphthae that do not respond to topical therapy

**Systemic Corticosteroids**

<table>
<thead>
<tr>
<th>CORTICOSTEROID</th>
<th>EQUIVALENT DOSE (mg)</th>
<th>GLUCOCORTICOID POTENCY</th>
<th>BIOLGIC HALF-LIFE (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SHORT-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisone</td>
<td>25</td>
<td>0.8</td>
<td>8-12</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20</td>
<td>1</td>
<td>8-12</td>
</tr>
<tr>
<td><strong>INTERMEDIATE-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>5</td>
<td>4</td>
<td>24-36</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>4</td>
<td>24-36</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>5</td>
<td>24-36</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4</td>
<td>5</td>
<td>24-36</td>
</tr>
<tr>
<td><strong>LONG-ACTING</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>20-30</td>
<td>36-54</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>0.6 – 0.75</td>
<td>20-30</td>
<td>36-54</td>
</tr>
</tbody>
</table>

**Daily Cortisol Production**

- 20-30 mg (equivalent to 5 - 7.5 mg prednisone)
- 50-75 mg minor stress production
- 300 mg maximum stress production

**Excess Glucocorticoid Production (Cushing Disease)**
**Prognosis**
- Excellent
- Variable recurrences

**Lichen Planus**

**Etiology**
- T-cell mediated autoimmune damage to basal keratinocytes that express altered self-antigens on their surface
- Multiple potential triggers
  - Hepatitis C; HBV immunization
  - Primary biliary cirrhosis
  - Other viruses – HHV-6, HHV-7
  - Contact allergens
  - Drugs

**Epidemiology**
- Middle age
- Females >> males
- Exacerbated by “stress”

**Clinical Features (Skin)**
- Purple, polygonal, pruritic papules
- Peripheral Wickham’s striae
- Flexor wrists, dorsal hands, ankles, feet, thighs, glans penis
- >65% with oral lesions

**Clinical Features (Nails)**
- 10% of patients
  - May be the only feature in children
  - Lateral thinning
  - Longitudinal ridging and splitting
  - Onycholysis
  - Red lunula
  - Pterygium formation
Clinical Features (Genital)

Clinical Features (Esophagus)

Clinical Features (Oral)
- Widespread involvement
  - 75% buccal mucosa and tongue
  - 20% labial mucosa and gingiva
  - <5% palate and floor of mouth
  - <35% with skin lesions
- Multiple clinical forms
  - Reticular/plaque forms - asymptomatic
  - Erosive/atrophic/bullous forms - symptomatic

Differential Diagnosis
- Leukoplakia
- Lupus erythematosus
- Aphthous ulcers
- Pemphigus vulgaris
- Cicatricial pemphigoid
- Erythema multiforme

Diagnosis
- Biopsy is mandatory
- Routine histopathology
- Direct immunofluorescence
  - BMZ fibrinogen to rule out LE

Treatment
- No treatment for asymptomatic cases
- Corticosteroids
- Antimetabolites
- Dapsone
- Cyclosporine
- Occlusive dressings
Calcineurin Inhibitors

Creative Solutions

Prognosis
- Good prognosis
- Moderate morbidity (symptomatic forms)
- Exacerbations and remissions
- (?) premalignant potential
  - <2%
  - Lichenoid dysplasia

Mucous Membrane Pemphigoid

Also Known As . . .
- benign mucous membrane pemphigoid (but it’s not a neoplasm)
- cicatrical pemphigoid (but oral lesions rarely scar)
- ocular pemphigus (no relationship to pemphigus)
Etiology and Epidemiology
- Auto-immune phenomenon
  - Attack basement membrane proteins
  - BP-180; epiligrin (laminin-5); other
- Middle-age
- Females >> males

Clinical Features (Skin)
- Skin lesions uncommon
- Face, neck and upper trunk
- Scalp
  - Scarring
  - Atrophy
  - Alopecia

Clinical Features (Mucosa)
- Mucosal lesions common
  - Oral
  - Ocular (symblepharon)
  - Genital

Clinical Features (Ocular)

Clinical Features (Oral)
- Pain
- Gingival erythema
- Intact blisters rare
- Scarring uncommon
- Variable Nikolsky’s sign

Differential Diagnosis
- Periodontal disease
- Pemphigus vulgaris
- Lichen planus
- Erythema multiforme
- Primary herpetic gingivostomatitis
Diagnosis
- Routine biopsy
  - Sub-basilar cleft
  - No acantholysis
  - No Tzanck cells
- Direct immunofluorescence
  - IgG and C3 at the BMZ
- Indirect immunofluorescence not useful

Treatment
- Corticosteroids
- Antimetabolites / immunosuppressants
  - Dapsone
  - Cyclophosphamide (Cytoxan®)
  - Azathioprine (Imuran®)
  - Calcineurin inhibitors (Tacrolimus®)
  - Tetracycline and niacinamide (B3)
  - Thalidomide (Thalomid®)
- Ophthalmology consult

Thalidomide

Prognosis
- Good
- Exacerbations and remissions
  - No mortality

Etiology and Epidemiology
- Human Herpes Virus 1 (HHV-1)
- #2 most common viral disease
- Majority of individuals in USA exposed
- 50% of individuals give history of contact
- 15% asymptomatic shedders

Recurrent Herpes Simplex
Clinical Features

- Prodrome
  - Burning
  - Itching
  - Tingling
- Recurrences due to stress
  - Trauma
  - Emotion
  - Endocrine

Clinical Features

- Herpetiform cluster of vesicles
  - Vermilion border
  - Attached gingiva
  - Hard palate
- Infectious for 5-7 days
- Heal in 14 days

Differential Diagnosis

- Impetigo
- Recurrent aphthous ulcers
- Traumatic ulcers
- Other viral stomatitis

Diagnosis

- History
- Clinical signs and symptoms
- Serology
- Viral culture
- Tzanck test

Treatment

- Non-prescription topical antiviral drugs
  - Abreva®
- Prescription topical antiviral drugs
  - Denavir®
  - Zovirax®
- Prescription systemic antiviral drugs
  - Zovirax®
  - Famvir®
  - Valtrex®

Antivirals
Candidiasis

Etiology and Epidemiology
- Candida albicans
- Most common fungal infection
- 35% of healthy adults
- 90% of denture wearers
- Females > males

Treatment
- OTC remedies
- Iontophoresis
- Do not use corticosteroids

Lysine

Topical Antivirals

Systemic Antivirals
Predisposing Factors
- Antibiotics
- Xerostomia
- Immunodeficiency
  - Infancy
  - Antimetabolites
  - Acquired
- Malnutrition
- Endocrine dysfunction
  - Diabetes mellitus
  - Pregnancy
  - Oral contraceptives
  - Corticosteroids

Pseudomembranous Candidiasis
- Infants and debilitated adults
- White, non-adherent plaques
- Erythematous base
- Stomatopyrosis
- Stomatodynia

Differential Diagnosis
- Chemical burn
- Allergy
- Hypersensitivity
- Mucous patch
- Morsicatio buccarum / lingualis / labialis

Erythematous candidiasis
- Most common form
- Diffuse erythema
- Variable symptoms
- “denture sore mouth”
  - Limited to denture bearing mucosa
  - Frequently painless

Perlèche
- Angular cheilitis
- Moist, macerated, cracked
- Variable symptoms
- (?) role of decreased vertical dimension
- (?) role of vitamin B complex deficiency

Median Rhomboid Glossitis
- Not a congenital defect
- Posterior dorsal tongue
- Red, depapillated area
- Frequently painless
- Unknown significance
Differential Diagnosis
- Erosive / atrophic lichen planus
- Chemical burn
- Allergy / hypersensitivity
- Impetigo
- Geographic tongue

Diagnosis
- Smear
- Culture
- Biopsy
- Latex agglutination

Treatment
- Topical antifungals
- Systemic antifungals
- Topical antimicrobials

Topical Antifungals
- Nystatin (Mycostatin®)
  - Oral suspension
  - Pastilles
  - Vaginal suppositories
  - Cremes and ointments
- Clotrimazole (Mycelex®)
  - Troche
  - Cremes and ointments

Systemic Antifungals
- Ketoconazole (Nizoral®)
- Fluconazole (Diflucan®)
- Itraconazole (Sporanox®)

Topical antimicrobials
- Gentian violet
- Chlorhexidine
  - Peridex
  - Periogard
  - Paroex
Prognosis

- Excellent prognosis
- Frequent recurrences
- Treat predisposing factors

Oral Cancer

References

New Oral Cancer Cases and Deaths – 2014

<table>
<thead>
<tr>
<th>Estimated Number* of New Cancer Cases and Deaths by Sex, US, 2014</th>
<th>Estimated New Cases</th>
<th>Estimated Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both sexes</td>
<td>Male</td>
</tr>
<tr>
<td>All sites</td>
<td>1,945,520</td>
<td>968,800</td>
</tr>
<tr>
<td>Oral cavity &amp; oropharynx</td>
<td>658,340</td>
<td>350,440</td>
</tr>
<tr>
<td>Oral tongue</td>
<td>119,530</td>
<td>64,280</td>
</tr>
<tr>
<td>Oral tongue, floor of mouth</td>
<td>11,800</td>
<td>6,880</td>
</tr>
<tr>
<td>Other oral cavity</td>
<td>2,320</td>
<td>1,380</td>
</tr>
</tbody>
</table>

Risk Factors

- Intrinsic
  - Nutrition
  - Anemia
  - Immunosuppression
  - Oncogenes
Risk Factors
- Extrinsic
  - Tobacco
  - Alcohol
  - Tobacco AND alcohol (40x risk)
  - Ultraviolet radiation
  - Microbes

Tobacco Advertising
- Increased graphic warnings for cigarettes scheduled for September 2012
- Congress told the images would be frightening and disturbing to smokers
- Died a “political death”

Smoking Alternatives
- Smokeless (spit) tobacco
- Snus
- Hookah pipes
- E-cigarettes

Smokeless (Spit) Tobacco
- Mouth, tongue, cheek, gum, and throat cancer
- Esophageal cancer
- Stomach cancer
- Pancreatic cancer
- Increase in risk of heart disease, heart attacks, and stroke
- Addiction to nicotine
- Leukoplakia
- Gingivitis and gingival recession
- Periodontal bone loss
- Tooth abrasion
- Dental caries
- Tooth loss
- Stained and discolored teeth
- Bad breath

Smokeless (Spit) Tobacco

Guide to Quitting
Smokeless Tobacco

Snus
Hookah Pipes

E-cigarettes / -cigars / -pipes

Frances Willard
W.C.T.U. President (1879-1898)

Carrie Nation (1846-1911)

Unhealthy Alcohol Use

<table>
<thead>
<tr>
<th>Category of Use</th>
<th>Prevalence</th>
<th>Definition and Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risky use</td>
<td>30%</td>
<td>&gt;65 years: &gt;7 drinks/week or &gt;3 drinks/occasion&lt;br&gt;_&lt;65 years: &gt;14 drinks/week or &gt;4 drinks/occasion</td>
</tr>
<tr>
<td>Problem drinking</td>
<td>Varies</td>
<td>Alcohol-related consequences, e.g., &quot;hangover&quot;</td>
</tr>
<tr>
<td>Alcohol abuse, harmful use</td>
<td>5%</td>
<td>Failure to fulfill major role obligations; use in hazardous situations; alcohol-related legal problems; social or interpersonal problems</td>
</tr>
<tr>
<td>Alcohol dependence, alcoholism</td>
<td>4%</td>
<td>Clinically significant impairment or distress, plus 3 or more of the following: tolerance, withdrawal, excessive time spent obtaining, using or recovering from use, drinking more or longer than intended, inability to control use, continued use despite problems</td>
</tr>
</tbody>
</table>

Saitz R. NEJM 2005;352:596-607

Ultraviolet Radiation
Human Papillomavirus

- Epitheliotropic DNA virus
- >120 HPVs
  - Common warts – HPV 2, 7
  - Plantar warts – HPV 1, 2, 4, 63
  - Flat warts – HPV 3, 8, 10
  - Anogenital warts – HPV 6, 11, 42, 44
  - Anal lesions – HPV 6, 16, 18, 31, 53, 58

Human Papillomavirus

- >120 HPVs (continued)
  - Genital cancers –
    - HPV 16, 18, 31, 45 (highest risk)
    - HPV 33, 35, 39, 51, 52, 56, 58, 59 (high risk)
    - HPV 26, 53, 66, 68, 73, 82 (? high risk)
  - F.E.H. (Heck’s disease) – HPV 13, 32
  - Oral papillomas – 6, 7, 11, 16, 32
  - Laryngeal papillomatosis – 6, 11
  - Oropharyngeal cancer – 16, 18

HPV Epidemiology

- 20 million Americans are HPV+
- 6 million new cases annually
- 50% of sexually active adults will be HPV+ in their lifetime
- 33,000 HPV-related malignancies annually
- 12,000 HPV-related oral malignancies annually (36.4 percent of cases)

HPV Epidemiology

- 560,000 new cancers world-wide (5.2%)
- HPV 16 and 18 associated with 99.7% of all cervical cancers
- HPV 16, 18, 31, 35 are “high risk” for genital cancers
- HPV 16 associated with oropharyngeal cancer

HPV Prevalence

- Peaks with sexual activity
  - 14-19 year olds – 24.5% HPV+
  - 20-24 year olds – 44.8% HPV+
  - 25-29 year olds – 27.4% HPV+
  - 30-39 year olds – 27.5% HPV+
  - 40-49 year olds – 25.2% HPV+
  - 50-59 year olds – 19.6% HPV+
  - 14-59 year olds – 26.8% HPV+ (average)

HPV Transmission

- Perinatal transmission rare
  - HPV 6 and 11 -> respiratory papillomatosis
- Venereal transmission
  - Penile-vaginal
  - Penile-anal (17-31X in gay/bisexual men)
  - Oral
**HPV Transmission**
- A female college freshman who has one sex partner per year for four years has >85% probability of graduating with an HPV infection
- Hands
  - Self-inoculation of hands from genitalia and vice versa
  - Cross-inoculation of hands from genitalia and vice versa
  - No role for non-sexual hand contact
- Shared objects
- Blood
- Environmental surfaces, e.g., floor (plantar warts)

**HPV Transmission**
- Infection through micro-abrasion or other trauma
- Limited to basal cells of stratified squamous epithelium
- Released when epithelial cells desquamate
- Survive for months on environmental surfaces

**HPV Infection**
- Most infections cleared by the immune system
  - 97-100% of high-risk HPV infections cleared in 18 months
  - Persistent infection may lead to cancer

**HPV-related Cancers**

<table>
<thead>
<tr>
<th>SITE</th>
<th>ANNUAL</th>
<th>HPV</th>
<th>HPV 16/18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>12,000</td>
<td>11,500</td>
<td>9,100</td>
</tr>
<tr>
<td>Vulvar</td>
<td>3,100</td>
<td>1,600</td>
<td>1,400</td>
</tr>
<tr>
<td>Vagina</td>
<td>700</td>
<td>500</td>
<td>400</td>
</tr>
<tr>
<td>Penis</td>
<td>1,000</td>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>Anus</td>
<td>4,700</td>
<td>4,500</td>
<td>4,200</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>11,700</td>
<td>7,400</td>
<td>7,000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>33,400</strong></td>
<td><strong>25,900</strong></td>
<td><strong>22,600</strong></td>
</tr>
</tbody>
</table>

**HPV and Oral Cancer**
- PubMed (10/31/12)
  - Human papillomavirus + oral
  - 501 published manuscripts
- PubMed (3/24/13)
  - Human papillomavirus + oral
  - 2075 published manuscripts
- PubMed (11/1/14)
  - Human papillomavirus + oral
  - 6188 published manuscripts
What does the data show?

- HPV is an *independent* risk factor for oral and oropharyngeal squamous carcinoma
  - Multiple studies; multiple institutions
  - ~30% prevalence rate of HPV detection in H&N cancer surgical specimens
  - Higher prevalence in oropharyngeal lesions (~35%) than laryngeal (~25%) or oral (<25%) lesions

HPV and Oral Cancer

- Dramatic increase in HPV-related oral cancers
  - 0.8 cases per 100,000 population (1988)
  - 2.6 cases per 100,000 population (2004)
- More common in men
- Thought to be due to increased incidence of oral sex

Which HPV is responsible?

- HPV-16
  - 86.7% of oropharyngeal lesions
  - 68.2% of oral lesions
  - 69.2% of laryngeal lesions

Is HPV-related H&N SCC different?

- Yes
  - Better prognosis
  - Better clinical outcome

Human Papillomavirus in HNSCC: Recognition of a Distinct Disease Type

Laura Vidal, MD, Maura L. Gillison, MD, PhD
Sex & Oropharyngeal Cancer

- Sexual behavior is associated with oropharyngeal carcinoma
- Related to lifetime # of sex partners
  - Vaginal sex and oral sex
  - Open-mouth kissing
- HPV exposure precedes oropharyngeal cancer by at least 10 years

How big is the problem?

Prevalence of Oral HPV Infection in the United States, 2009-2010

Conclusion: Among men and women aged 14 to 69 years in the United States, the overall prevalence of oral HPV infection was 6.9%, and the prevalence was higher among men than among women.

HPV Vaccines

- Bivalent (HPV 16 and 18) and quadrivalent (HPV 16, 18, 6 and 11)
- Little benefit to previously infected individuals
- 49% of teenage girls in USA vaccinated in 2010

HPV Vaccines – 3 Injections

Cervarix
- Bivalent
- Females 9-25
- Cervical cancer (HPV 16, 18)

Gardasil
- Quadrivalent
- Females and males 9-26
- Cervical cancer (HPV 16, 18)
- Genital warts (HPV 6, 11)
Unanswered Questions

- Do we treat HPV-positive premalignant, i.e., dysplastic, oropharyngeal lesions differently?
- Do we treat HPV-positive malignant oropharyngeal lesions differently?
- Would some oropharyngeal cancers be prevented by HPV vaccination?

Even more questions with no answers

- If a latent infection reappears, how does your spouse know it’s not a “new” infection?
- Who should be tested? Everybody?
- Is HPV positivity in an adolescent a marker for sexual activity?
- When do you recheck an HPV+ patient?
- How about the rest of the family?

Questions with no answers

- Is HPV transmitted by kissing? Deep kissing? How deep? How do you test this?
- If HPV is transmitted by kissing, are you “giving” someone oral cancer.
- Is there a risk of mother-child transmission?

Clinical Features

- 90% of cases
  - lower lip
  - ventral tongue
  - floor of mouth
- Most cases present for at least 1 year as an asymptomatic lesion
Clinical Features
- Leukoplakic (white)
- Endophytic (ulcerating)
- Exophytic (fungating)
- Erythroplakic (red)

Diagnostic Techniques
- Scalpel biopsy
- Punch biopsy

Therapeutic Modalities
- Multidisciplinary Therapy
  - Surgery
  - Radiation therapy
  - Combination therapy
  - Periodic reassessment

Prognosis
- Depends on location and progression
- More anterior location
- No regional lymph node involvement
- No distant metastasis

Grading
- Assessment of biologic behavior based on microscopic features of pleomorphism, cellular maturation, keratin production, etc.
- Grade I – well differentiated
- Grade II – moderately well differentiated
- Grade III – moderately differentiated
- Grade IV – poorly differentiated
**Staging**

- Assessment of survival based on a combination of factors
  - tumor size (T)
  - regional lymph node involvement (N)
  - distant metastasis (M)
- TNM system

**TNM Staging**

- TX – not assessed
- T0 – no evidence of tumor
- Tis – carcinoma *in situ*
- T1 – <2 cm
- T2 – 2-4 cm
- T3 – >4 cm
- T4 – invading adjacent structures

**TNM Staging**

- NX – not assessed
- N0 – no nodal involvement
- N1 – single, ipsilateral node, <3 cm
- N2 – nodal metastasis, 3-6 cm
- N2a – single, ipsilateral node, 3-6 cm
- N2b – multiple ipsilateral nodes, <6 cm
- N2c – bilateral or contralateral nodes, <6 cm
- N3 – nodal metastasis, >6 cm

**TNM Staging**

<table>
<thead>
<tr>
<th>TNM</th>
<th>STAGE</th>
<th>5 YEAR SURVIVAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1N0M0</td>
<td>Stage I</td>
<td>85%</td>
</tr>
<tr>
<td>T2N0M0</td>
<td>Stage II</td>
<td>66%</td>
</tr>
<tr>
<td>T3N0M0</td>
<td>Stage III</td>
<td>41%</td>
</tr>
<tr>
<td>T1-3N1M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any T4</td>
<td>Stage IV</td>
<td>9%</td>
</tr>
<tr>
<td>Any N2-3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any M1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Iatrogenic Xerostomia**
Etiology

- Drug side-effect
- Prescription medications
  - Antidepressants
  - Antihypertensives
  - Psychotherapeutic agents
- OTC medications
  - Antihistamines
- Head and neck radiation therapy
- Nocturnal mouth breathing

Antidepressants

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RANK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prozac® (fluoxetine)</td>
<td>9</td>
</tr>
<tr>
<td>Zoloft® (sertraline)</td>
<td>13</td>
</tr>
<tr>
<td>Paxil® (paroxetine)</td>
<td>33</td>
</tr>
<tr>
<td>Elavil® (amitryptiline)</td>
<td>47</td>
</tr>
<tr>
<td>Pamelor® (nortriptyline)</td>
<td>163</td>
</tr>
<tr>
<td>Effexor® (venlaxafine)</td>
<td>180</td>
</tr>
</tbody>
</table>

Antihypertensives

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RANK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyazide® (triamterene/HCTZ)</td>
<td>17</td>
</tr>
<tr>
<td>Lasix® (furosemide)</td>
<td>23</td>
</tr>
<tr>
<td>Esidrix® (hydrochlorothiazide)</td>
<td>94</td>
</tr>
<tr>
<td>Tenormin® (atenolol)</td>
<td>116</td>
</tr>
</tbody>
</table>

Psychotherapeutic Agents

<table>
<thead>
<tr>
<th>DRUG</th>
<th>RANK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xanax® (alprazolam)</td>
<td>38</td>
</tr>
<tr>
<td>Klonopin® (clonazepam)</td>
<td>48</td>
</tr>
<tr>
<td>Ativan® (lorazepam)</td>
<td>79</td>
</tr>
<tr>
<td>Valium® (diazepam)</td>
<td>133</td>
</tr>
<tr>
<td>Restoril® (temazepam)</td>
<td>149</td>
</tr>
</tbody>
</table>

Epidemiology

- One of the most common drug side effects
Nocturnal Mouth Breathing

Clinical Features
- Identical to Sjögren's syndrome
- Temporal relationship to medication use
- Resolution when medication changed or dosage regimen altered

Differential Diagnosis
- Sjögren's syndrome

Diagnosis
- By exclusion

Treatment
- Change medication
- Alter dosage regimen
- Sialogogues
- Artificial saliva

Salivary Stimulants
- OTC sialogogues
  - Sugarless candy
  - Sugarless gum
Treatment
- Water
- Artificial saliva / moisturizers
  - MedOral®
  - Salivart®
  - Oasis®
  - Glandosane®
  - Mouthkote®
  - Oral Balance gel®
- Ethyol® (amifostine) – IV before XRT
- Salivary stimulants
  - Salagen® (pilocarpine)
  - Evoxac® (cevimeline)
  - Urecholine® (bethanechol)
- Topical fluoride
  - Prevident® (1.1% neutral NaF)
  - NeutraCare® (1.1% neutral NaF)

Side Effects
- Sweating
- Lacrimation
- Urinary frequency

Dental Caries
- Aggressive therapy
  - Scrupulous oral hygiene
  - Dietary alterations
  - Chlorhexidine mouth rinses
  - Topical fluoride
  - Salivary stimulation

Prognosis
- Variable
- Excellent if medication can be changed or dosage altered
- Poor if permanent damage (radiation)