Appropriate Chemotherapeutics for the Advanced Periodontal Patient

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Appropriate Chemotherapeutics for the Advanced Periodontal Patient

Goals of Dental Care
- health
- function
- esthetics

Dental Diseases Treated
- oral cancer
- dental caries
- periodontal disease

Probiotic Therapy
- Strep oralis
  - a naturally occurring oral bacteria
  - inhibits periodontal pathogens by releasing hydrogen peroxide

Probiotic Therapy
- Strep ubernis
  - a naturally occurring oral bacteria
  - found only in healthy perio sites
  - outcompetes perio pathogens

Probiotic Therapy
- aka replacement therapy
- out competes resident flora
- most oral PB are produced with GI tract flora
- one PB is produced with 3 human oral bacteria
Probiotic Therapy

*Strep rattus*
- a mutagenized form of *strep mutans*
- does not produce lactic acid
- outcompetes the indigenous *strep mutans* (*i.e.* replacement therapy)

What % of Your Patients Present with Periodontal Diseases

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National Health & Nutrition Examination Survey (NHANES)
- 46% of all adult Americans have periodontitis
- 64.7 million Americans > 30 yo have periodontitis
- 8.9% have severe periodontitis


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National Health & Nutrition Examination Survey (NHANES)
- 46% of all adult Americans have periodontitis
- 64.7 million Americans > 30 yo have periodontitis
- 8.9% have severe periodontitis
- prevalence is higher in males than females
- prevalence is highest in Hispanics (63.5%)
- 59.1% in blacks; 50.0% Asian; 40.8% whites
- 2 X higher in low socio-economic groups


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National Health & Nutrition Examination Survey (NHANES)
- 46% of adult Americans (64M) have periodontitis
- by comparison:
  - 24.6 million Americans have diabetes
  - 80 million Americans have heart disease
- prevalence may be associated with increasing life span while retaining more natural teeth
- 70.1% of Americans > 65yo have periodontitis


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70.1% of Americans > 65 years old have periodontitis

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What is Periodontal Disease?

Periodontium

Those tissues that invest and support the teeth
- Gingiva
- Periodontal ligament
- Cementum
- Alveolar bone

*AAP Glossary of Periodontal Terms; 1992 3rd Ed.*

Periodontal Diseases

Gingivitis
- Inflammation of the gingiva

Periodontitis
- Inflammation of the supporting tissues of the teeth, usually progressively destructive changes leading to loss of bone and periodontal ligament.

*AAP Glossary of Periodontal Terms*

Broad Categories of Periodontal Diseases

- Gingivitis 49%
- Periodontitis 46%

What is the greatest risk factor for dying of a heart attack?
What are some of risk factors associated with developing periodontitis?

?  

What are some of risk factors associated with having periodontitis?

What are some of risk factors associated with developing periodontitis?

- plaque

What percentage of your patients with periodontitis is plaque associated?

Plaque Control Modalities

*Intrinsic*
- saliva
- > 500 medications list xerostomia listed a side effect
- H&N radiation caused XS
- age related xerostomia
Plaque Control Modalities

**Intrinsic**
- other salivary reducing dz
  - diabetes
  - scleroderma
  - Parkinson's disease
  - Sjögren's syndrome

**Extrinsic**

**Toothbrush**
- for caries, modified Bass technique is desired
- manual vs powered TB
- a P-TB is 60% more effective interproximally & at the gingival margin than manual

**Dentifrice**
- for caries: ANY toothpaste with fluoride is desired
- where most plaque accumulates
- for perio dz: TP w/ substantivity
- triclosan provides substantivity

**Flossing (& power flossing)**
- toothbrushing + flossing is better than TB alone
- power-floss: waterpikging, etc
- TB + F > TB + P-F
  - BUT...
  - TB + P-F > TB alone

Plaque Control Modalities

**Intrinsic**
- immune response
- innate vs host susceptibility
- diseases affecting the innate immune response
- medications affecting host susceptibility (NSAIDs, chemo)
Plaque Control Modalities

**Mouth rinses**
- for caries: ANY mouthrinse with fluoride is desired
- for perio dx: antiseptic MR that penetrates the biofilm & that exerts bactericidal activity

**Extrinsic**
- methods to stimulate flow
- xylitol/sorbital oral rinses
- lozenges
- xylitol oral adhesive

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Laboratory Methods of Deriving an Accurate Periodontal Diagnosis

- About 800 bacterial species identified in perio pockets
- Only a few are clearly associated w/ progressive periodontitis, mostly subgingival species
- Periodontal lesions usually are a group of putative pathogens rather than a single pathogenic species

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Subgingival Plaque

Stabilizing flora
- Streptococcus
- Neisseria
- Corynebacteria
- Actinomyces

Superinfections
- Candida
- Enterobacteriaceae
- haem. streptococci
- Staphylococci aureus

Specific periodontal pathogens
- *A. actinomycetemcomitans*
- *N. gonorrhoeae*
- *P. gingivalis*
- *T. denticola*
- *F. nucleatum*
- *E. faecalis*


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Association between periodontal pathogens and periodontitis

Strong
- Porphyromonas gingivalis
- Treponema denticola
- Prevotella intermedia
- Eikenella corrodens
- *B. melanogenes*
- *P. gingivalis*
- *T. denticola*

Moderate
- *B. melanogenes*
- *P. gingivalis*
- *T. denticola*

Early Stage of Investigation
- gram-negative cocci
- fibroblastic cells
- neutrophilic
- eosinophils

Modified from Haffajee and Socransky and Slots and Chen. This list is not all-inclusive.
Position of the AAP about Microbiological Analysis

Clinical value:
- Identifying the presence of therapeutic targets (i.e., putative pathogens)
- Adjustment of the use of supportive antibiotics
- Monitoring the response to therapy
- Identifying sites at high risk for progression
- Determining a pt specific recall interval

Methods of Microbial Diagnosis
- Classically microbiologic sampling
- Previous "Gold-Standard"
- Prerequisite for in-vitro sensitivity testing
- Time consuming
- Expensive
- Limited survival time of sampled bacteria → false negative results

Methods of Microbial Diagnosis
- Molecular genetic technique / DNA-testing
- New Gold-Standard
- High sensitivity and specificity
- Fast and inexpensive
- Easy to handle sampling
- No limitation of transport

What are some of risk factors associated with developing periodontitis?
- Plaque
- Age
- Sex
- Ethnic background
- Genetic susceptibility
- Systemic disease
- Stress
- Smoking

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What are some of the risk factors associated with developing periodontitis?

- Plaque
- Age
- Sex
- Ethnic background
- Genetic susceptibility
- Systemic disease
- Stress
- Smoking

What are some approaches for treatment of periodontitis?

- Traditional periodontal therapy
  - Scaling & root planing

What are some of the risk factors associated with having periodontitis?

- Occlusion
  - Guards
  - Onabotulinumtoxin A
What are some approaches for treatment of periodontitis?

- Traditional periodontal therapy
- Rationale for pharmacologic agents

What are some approaches for treatment of periodontitis?

- Traditional periodontal therapy
- Rationale for pharmacologic agents
  - periodontal pathogens also have been found to invade soft tissue and bone
  - aggressive forms of periodontal disease have more likelihood of having invasive bacteria
  - debridement of root surface who addressing the invasiveness of the disease allows for re-inoculation of the root surface
  - lead to the use of concomitant antibiotic therapy


What are some approaches for treatment of periodontitis?

The FDA cleared the Nd-YAG laser and protocol for periodontal regeneration

don't have to touch the cells / tissue to have an affect
What are some approaches for treatment of periodontitis?

- Traditional periodontal therapy
- Rationale for pharmacologic agents
  - use of Ab therapy is not a replacement for conventional tx
  - not all periodontal diseases will respond to conventional tx alone even if provided ideally
  - aggressive forms of periodontal disease progress more rapidly than chronic non-aggressive periodontal disease
  - require more aggressive treatment

Systemic Delivery Pharmacotherapeutics

- Tetracyclines*
  - Tetracycline
  - Doxycycline
  - Minocycline
  - Metronidazole
  - Amoxicillin
  - Erythromycin

  - general concern for:
    - developing resistant flora
    - sensitivity & allergy issues

Systemic Delivery Pharmacotherapeutics

- Periodontal disease & smoking
  - 25% of US adults smoke
  - 50% of all periodontal disease cases can be attributed to smoking independent of all other risk factors
  - smoking is the major preventable risk factor for periodontitis in the US adult population
  - current smokers: 4 X risk
  - former smokers: 2 X risk
  - < 9 / day: 3 X risk
  - > 31 / day: 6 X risk
  - quit > 11 years: same risk as non-smokers


- Rationale for use
  - bacterial infection releases microbial factors LPS, antigens
  - induces host inflammatory response
  - releases IL-1, TNF-α, PGE2
  - host cells release collagenases 1, 2, 3
  - collagenase 1 (MMP-1) by Fb
  - collagenase 2 (MMP-8) by neutrophils
  - collagenase 3 (MMP-13) by osteoclast
  - situations when conventional tx does not achieve desired result
  - patients with non-microbial risk factors (e.g., smoking, diabetes or genetic predisposition)
  - in these instances use of host-modulatory tx in conjunction with traditional treatment may be advantageous

Systemic Delivery Pharmacotherapeutics

- Periodontal disease & smoking
  - smokers may have more virulent types of bacteria
  - oxygen tension levels support anaerobic infection
  - altered host defense mechanisms via white cell function
  - decreased WBC phagocytosis (ability to move through tissue in response to infection)
  - smokers have impaired wound healing
  - nicotine decreases blood flow in gingival tissue
  - decreased blood flow => ↓ nutrient supply
  - smoking ↑ pro-inflammatory cytokine production
  - IL-6, TNFα, IL-1, PGE2
  - results in ↑ tissue-destructive enzyme activity

Systemic Delivery Pharmacotherapeutics

- Periodontal disease & smoking
  - multiple studies have confirmed
  - non-surgical & surgical therapy is less effective in smokers
  - recurrence of dz after tx is more likely in smokers
  - smokers only achieve ~ 50% of benefit from periodontal therapy
  - traditional therapy only addresses bacterial component
  - in these instances use of host modulatory tx in conjunction with traditional treatment may be advantageous

Systemic Delivery Pharmacotherapeutics

- 20 mg Doxycycline
  - submicrobial dosage
  - does not promote Ab resistance
  - binds to the lipopolysaccharides that bacteria releases
  - good for patients that are compromised
  - used as an adjunct to therapy for patients that are smokers, diabetics, otherwise compromised
  - as an adjunct to surgical therapy

Systemic Delivery Pharmacotherapeutics

- DCN 20mg
  - evaluated 210 adult periodontitis patients, 70% smokers or recent ex-smokers
  - 8 month, double-blind, multi-center (8 dental schools), placebo-controlled study
  - SCL / RP 1 H / qued
  - clinical measurements @ 1, 3, 5, 8 months
  - measurements & retreatment if necessary @ 1, 3, 5, 8 mo

Systemic Delivery Pharmacotherapeutics

- Doxycycline Plasma Concentrations - Steady-State

Doxycycline Plasma Concentrations (ng/mL)

<table>
<thead>
<tr>
<th>Hours</th>
<th>Minimum antimicrobial dose</th>
<th>Sub-antimicrobial dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.4</td>
<td>0.4</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>0.8</td>
</tr>
<tr>
<td>6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>8</td>
<td>0.6</td>
<td>1.2</td>
</tr>
<tr>
<td>10</td>
<td>0.4</td>
<td>1.4</td>
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<tr>
<td>12</td>
<td>0.2</td>
<td>1.5</td>
</tr>
<tr>
<td>14</td>
<td>0.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Systemic Delivery Pharmacotherapeutics

- All teeth with baseline PD > 7mm

Mean PD Change (mm)

<table>
<thead>
<tr>
<th>Time</th>
<th>DCN 20mg Mean</th>
<th>Placebo Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.35</td>
<td>1.41</td>
</tr>
<tr>
<td>1 month</td>
<td>2.91</td>
<td>3.02</td>
</tr>
<tr>
<td>3 months</td>
<td>3.55</td>
<td>3.05</td>
</tr>
<tr>
<td>5.25 months</td>
<td>2.95</td>
<td>3.01</td>
</tr>
<tr>
<td>8 months</td>
<td>2.52</td>
<td>2.99</td>
</tr>
</tbody>
</table>

* p < 0.05

### Systemic Delivery Pharmacotherapeutics

**Molar teeth with baseline PD > 7mm**

![Graph showing mean PD change over time with DCN 20mg and Placebo groups](image)

- DCN 20mg & Diabetes
  - effect of Periostat on periodontal therapy & diabetic control in patients with type 1 and type 2 diabetes
  - 2 groups: Group 1 - SCL / RP only
  - Group 2 - SCL / RP + Periostat x 3mo
  - re-evaluation at 6 & 12 weeks
  - evaluated PD, BOP, HbA1c, etc.

(From: Ciancio, S. et al. AADR 2003.0074)

### Systemic Delivery Pharmacotherapeutics

**Glycemic Control**

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Baseline</td>
</tr>
<tr>
<td>% HbA1c Change</td>
<td>Placebo n=10</td>
</tr>
<tr>
<td>6.31 ± 0.30</td>
<td>7.22 ± 0.38</td>
</tr>
<tr>
<td>5.94 ± 0.44</td>
<td>7.17 ± 0.23</td>
</tr>
<tr>
<td>6.09 ± 0.36</td>
<td></td>
</tr>
</tbody>
</table>

### Local Delivery Pharmacotherapeutics

- Benefit of local delivery pharmacotherapeutic for treatment of periodontal diseases
  - improved concentration of medication
  - site specificity
  - increased compliance


### Local Delivery Pharmacotherapeutics

- Benefit of local delivery pharmacotherapeutic for treatment of periodontal diseases
  - subgingival bacteria exist within a biofilm which is relatively impervious to any Ab unless thoroughly disrupted
  - used in conjunction with conventional therapy
  - certain bacterial species survive Ab cond
  - 2μg/mL (2,000 μg/mL) in a biofilm
  - this is 500 - 1000X greater than can be achieved in GCF via the use of systemic antibiotics


### Local Delivery Pharmacotherapeutics

- Benefit of local delivery pharmacotherapeutic for treatment of periodontal diseases
  - locally delivered doxycycline (DCN) gel applied to perio pocket
  - release data reveals DCN levels of 1,000 - 2,000 μg/mL
  - 24 H after placement in perio pocket
  - after 2 weeks, 100 μg/mL are detectable in the pocket
  - this level is considered bactericidal for most bacteria that are resistant to systemically delivered antibiotics
  - local delivery of antibiotic has negligible impact on the microflora of the remainder of the body
  - does not promote development of resistant flora

(Stoller NR, Johnson LR, Trapeff S, Harold CG, Garrett S. The pharmacokinetic profile of biodegradable DCN in GCF. J Periodontol 2002;73:1085-1091)
Local Delivery Pharmacotherapeutics

- Controlled / Sustained Release Devices
  - Available worldwide
    - impregnated fiber
    - metronidazole gel
    - minocycline ointment
    - chlorhexidine chip
    - doxycycline polymer
    - minocycline polymer

Local Delivery Pharmacotherapeutics

- Minocycline
  - is a potent broad-spectrum antibiotic
  - semi-synthetic derivative of tetracycline
  - effective against many putative periodontal pathogens

<table>
<thead>
<tr>
<th>Periodontal Pathogen</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroides Forssythus</td>
<td>4</td>
</tr>
<tr>
<td>Porphyromonas Gingivalis</td>
<td>1</td>
</tr>
<tr>
<td>Actinobacillus Actinomycetemcomitans</td>
<td>4</td>
</tr>
<tr>
<td>Prevotella Intermedia</td>
<td>4</td>
</tr>
<tr>
<td>Treponema Denticola</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Local Delivery Pharmacotherapeutics

![Graph showing concentration of 1mg minocycline HCl microspheres over time (months).](Image)

*Christersson et al. J Periodontol.*

Local Delivery Pharmacotherapeutics

1mg MCN HCl microspheres => Sustained PD ↓

![Graph showing change in pocket depth (mm) over time (months).](Image)

*Christersson et al. J Periodontol.*

Local Delivery Pharmacotherapeutics

1mg minocycline HCl microspheres => PD ↓

![Pie chart showing PD reduction.](Image)

61% of responding sites treated with SCL / RP + 1mg MCN exhibited PD reduction > 2mm or more

Expect 6 of 10 sites to respond ≥ 2mm

*Christersson et al. J Periodontol.*

Local Delivery Pharmacotherapeutics

1mg MCN HCl => > % Patients w/ PD < 5mm

![Bar chart showing percentage of patients.](Image)

26% more patients shifted below the 5mm threshold with MCN & SRP
Local Delivery Pharmacotherapeutics

1mg MCN HCl ⇒ PD ↓ in Smokers

- SCL / RP + 1mg MCN HCl microspheres demonstrated significant PD ↓ when compared to SCL / RP alone in:
  - smokers
  - patients > 50 years old
  - patients with a history of cardiovascular disease
  - patients with deeper pockets
  - molar teeth locations
  - mandibular locations

Role of anti-inflammatory therapy in managing Periodontal Disease

- Inflammation:
  - is self-perpetuating
  - alters susceptibility of the periodontium
  - is transient and only exists during an active infection
  - is genetically programmed to be hyperactive or resolution dependent

Possible indicators for periodontal inflammation

- Cytokines: Interleukins and tissue necrosing factors
- PGE2
- C Reactive Protein
- Glycated hemoglobin levels (HbA1c)

Managing Inflammation

- Decrease or change flora
- Utilize NSAIDs to target lipids and change the proinflammatory role
- Effect the destructive enzymes
- Address the oxidative process
- Modulate the host...
Periodontal Disease and Systemic Disease Links

Oxidation is a Natural Process in an Oxygen Rich Environment
Examples of Oxidation

Oxidation
- oxidative stress is caused by an imbalance between ROS activity & total antioxidant capacity
- oxidative stress incites an inflammatory response and plays a role in many chronic inflammatory diseases
- nicotine, alcohol, H2O2, and many materials used in dentistry increase free radical activity

What is Oxidative Stress
an imbalance between free radicals and the body's ability to readily detoxify reactive oxygen species (ROS)

What is Oxidative Stress
results from an increased production of oxidizing species or a decreased capability of antioxidant defenses

What is Oxidative Stress
results from an increased production of oxidizing species or a decreased capability of antioxidant defenses
What is Oxidative Stress

a cell can recover from mild or brief oxidative episodes

What is Oxidative Stress

more severe oxidative stress causes cell damage and eventually cell death

What is Oxidative Stress

Free Radical Pathway

Oxidative Stress' Role in all Oral Inflammatory Conditions

- Gingivitis
- Periodontitis
- Oral lichen planus
- Ulcers
- Migratory Glossitis
Oxidation

- specific combinations of antioxidants neutralize free radical activity and induce tissue repair
- topical application of specific antioxidants shows great promise for prevention and treatment of many oral conditions including:
  - xerostomia
  - gingival inflammation at crown margins
  - lichen planus
  - ulcers
  - BRONJ
  - post-surgical wound healing without the disadvantages of chlorhexidine

New Generation Oral Pharmaceuticals

<table>
<thead>
<tr>
<th>Topically Applied Antioxidants</th>
<th>Chlorhexidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-bacterial Effect</td>
<td>Anti-bacterial Effect</td>
</tr>
<tr>
<td>Anti-inflammatory Effect</td>
<td>Anti-inflammation Effect</td>
</tr>
<tr>
<td>No Teeth Staining</td>
<td>No Teeth Staining</td>
</tr>
<tr>
<td>High Patient Compliance</td>
<td>High Patient Compliance</td>
</tr>
</tbody>
</table>

Reference:

Pawlus MA, Oxford GE et al: Root Biomodification with Citric Acid or TCN. 2000;JDR 1287-1294.

Questions ???