Antibiotic & Antiseptic Use in Periodontal Therapy Part 1

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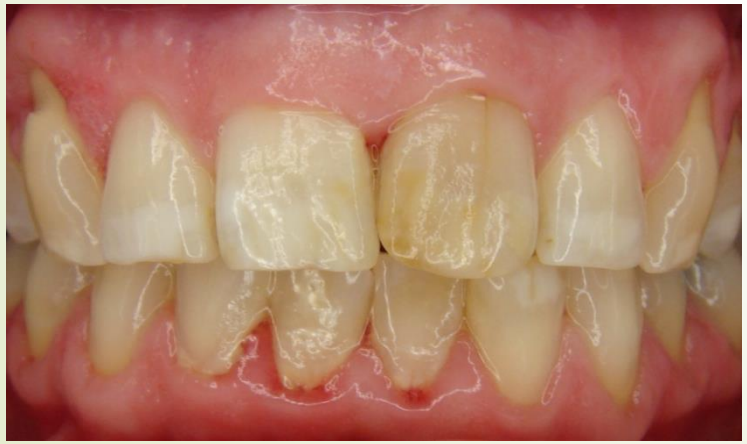
Introduction

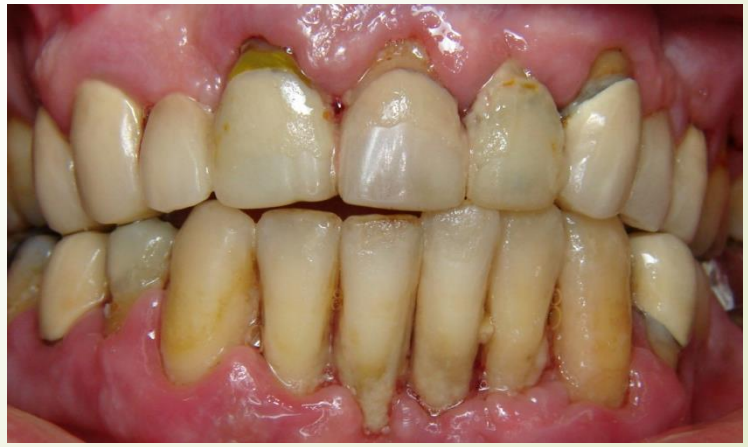
- Microbial aetiology

  (Bacteria within dental plaque biofilm)
- Bacteria essential but insufficient for development of periodontitis
- Host susceptibility – destructive immunoinflammatory response to subgingival plaque bacteria

Gingivitis



Periodontitis



Microbial Aetiology

- Over 600 species in subgingival flora
- Only a few species clearly associated with periodontitis
  - Aggregatibacter actinomycetecomitans (A.a)
  - Porphyromonas gingivalis (P.g)
  - Tanerella forsythensis (T.f)
  - Treponema denticola (T.d)

(Haffajee & Socransky 1994/1998)

- Many species still unidentified

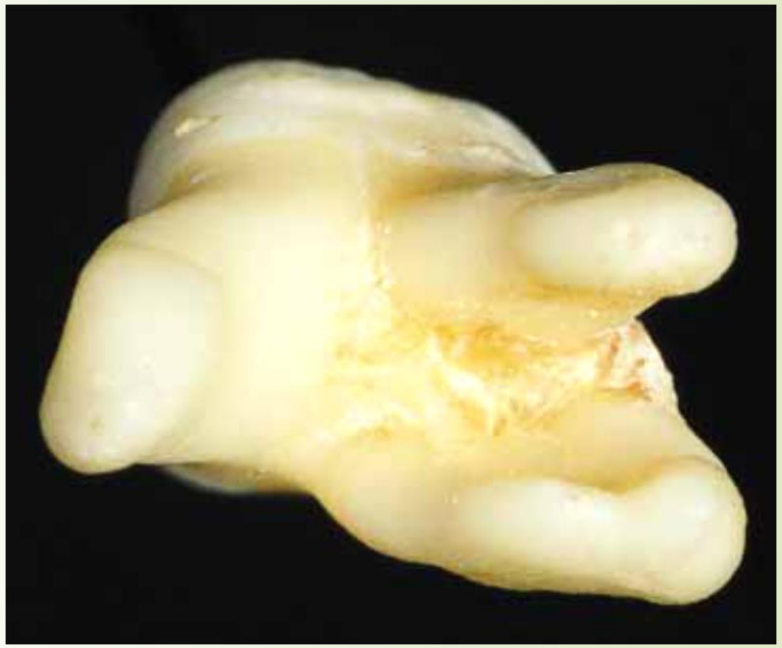
Periodontal Disease – Control ??

- Control host response modifying factors
- Elimination of plaque retentive factors
- Disruption and reduction of plaque biofilm
- Shift of microbial flora composition

Limitations of Treatment

- Local anatomy:

  Root concavities, grooves and furcations
- Bacterial invasion of gingival tissue
- Inability to disrupt biofilm and suppress bacteria to a level compatible with the host
- Reduced treatment outcome associated with elevated periodontopathogen levels
- May experience ongoing periodontal breakdown
  - Need for adjunctive therapy?
  - Antibiotic therapy?
  - Systemic or local delivery?



Antibiotic therapy

- Natural or synthetic organic substances that can inhibit or kill selective microorganisms

- Multi-million dollar industry
- In 1998, over 1.6 billion USD was spent on promotion
- In the USA, over 1 million kilograms of antibiotics are prescribed for human use annually

Bacterial Resistance

- Antibiotic use is a primary factor
- Intrinsic, mutational or acquired
- Selection of resistant species
  - Methicillin Resistant Staphylococcus aureus (MRSA)
  - Vancomycin Resistant Staphylococcus aureus (VRSA)

"What doesn't kill them makes them stronger"

Periodontal Bacterial Resistance

- Gram –ve species (Prevotella) produce β-lactamases
- β-lactamases detected in periodontal pockets
- Tetracycline resistance
- Resistance associated with increased antibiotic use

Bacterial Resistance in Dentistry

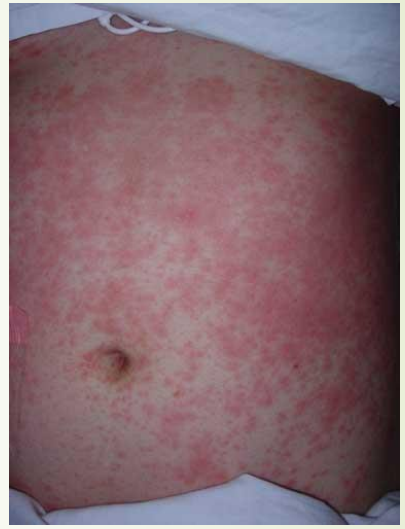
- Dentistry - approximately 10% of all antibiotic prescriptions
- Poor prescribing contributing to bacterial resistance
- Recent survey suggests:
  - 47% of dentists prescribed without a diagnosis
  - 30% of dentists prescribed due to time pressures

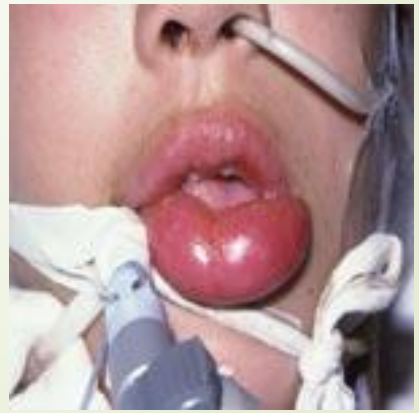
Bacterial Resistance – Prevention

- Judicious use of antibiotics
- Selection of:
  - Appropriate clinical scenario for antibiotic use
  - Appropriate agent for each clinical scenario

1. Antibiotics have the potential to cause harm

- Allergies and Hypersensitivities
  - 16% of all drug related adverse events presenting to the Emergency Department
  - Commonly Penicillin
  - Allergic reactions to Penicillin ranges from 0.7% to 10% among the general population
  - Anaphylaxis risk: 0.04-0.011%
  - Fatal anaphylaxis risk: 0.002%
  - Can develop at any exposure to drug





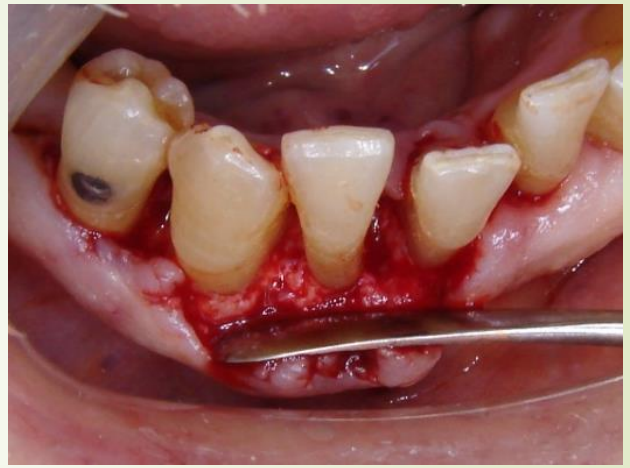
- Adverse Reactions
  - Nausea and Diarrhoea
- Opportunistic infections
  - Pseudomembranous colitis
  - Candidosis
- Drug interactions
  - Warfarin
  - Alcohol
- Toxicity
  - Teratogenic effects
  - Breastfeeding

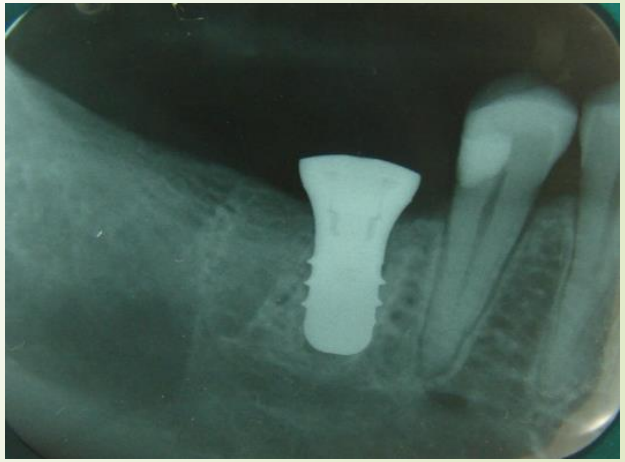
2. Antibiotics should be used in limited clinical situations

- Prophylaxis or Therapy
- Prophylaxis
  - Immunosuppressed individuals
  - Infective Endocarditis
    - Indications should be considered in light of recently updated guidelines
  - Prevention of postoperative infection???
  - Improve periodontal regenerative outcome???

Prevention of postoperative infection

- Antibiotics prescribed often for periodontal and implant surgery
- Rate of postoperative infection low
  <1% - 5%
- No advantage demonstrated in reducing postoperative infection after:
  - Gingivectomy
  - Osseous resective surgery
  - Mucogingival surgery
  - Osseous grafting
- Reduced infection rate when CHX used



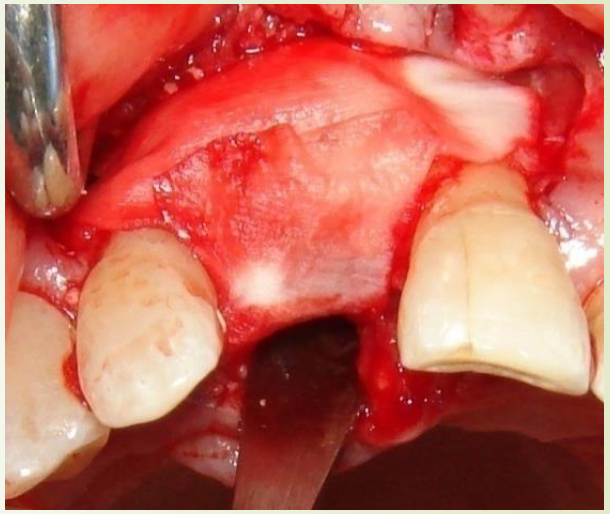


Implant surgery

- No difference in postoperative infection rates
- Role in reduction of implant failure controversial
  - Improved survival (2–4x higher)
  - No difference in survival
- Recent studies suggest
  - a single preoperative antibiotic dose more appropriate
  - Similar infection or survival rates when compared to pre- and postoperative regimen
- Cochrane review by Esposito et al.,(2008b) Metaanalysis of 2 RCT
  - Benefit of postoperative antibiotics unclear
  - 2g of Amoxicillin 1hr preoperatively
    - Significantly reduced early implant failures
    - No effect on postoperative infection

Implant surgery

Considerations for antibiotic prescription:



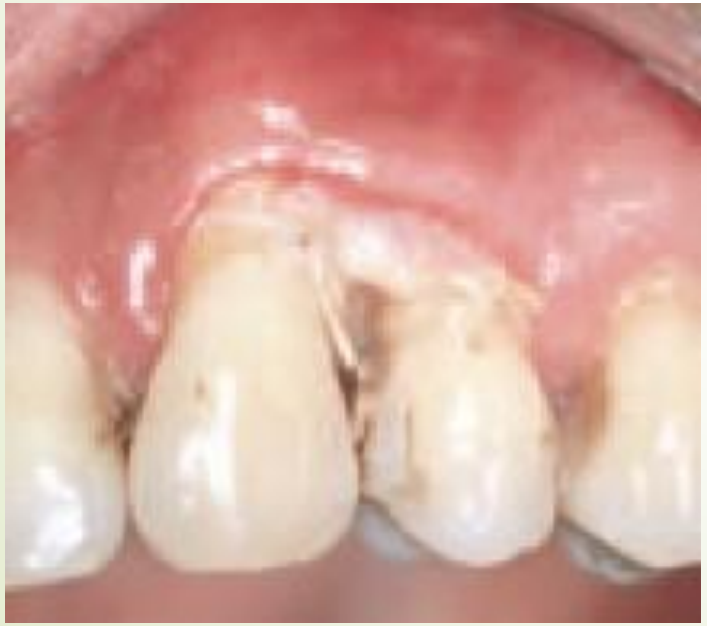
- Patient factors
- Level of asepsis
- Complicated or prolonged procedure
- Bone grafting
- Operator experience (<50 implants)
- Chlorhexidine mouthrinses reduce infection and implant failure

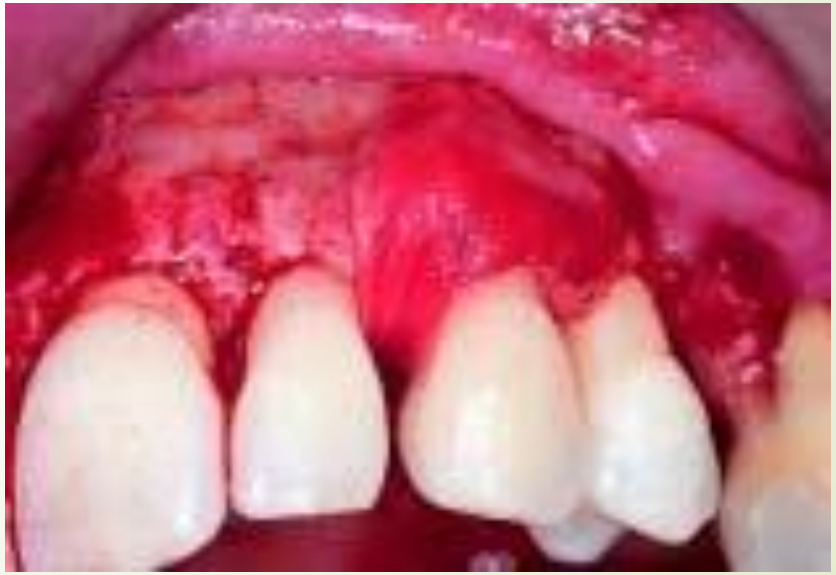
Periodontal regeneration

–Microbial colonisation of membrane associated with reduced CAL gain

Reduced clinical attachment loss gain

–Most studies have included systemic antibiotics during the first and/or second week of membrane placement





Periodontal regeneration

- Improved clinical outcomes with e-PTFE membranes in patients using systemic antibiotics compared to patients not receiving antibiotics

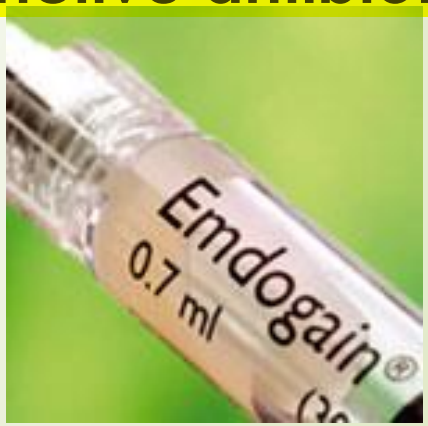
  Amoxicillin with Clavulanic Acid (Augmentin)

- No difference in clinical outcomes with Bioresorbable membranes

  Amoxicillin + Metronidazole

- Studies using Emdogain have utilised adjunctive antibiotics

  No additional benefits with adjunctive Amoxicillin and Metronidazole



- Antibiotics should not be used "just in case"
- No indication for routine periodontal surgery
- No indication for periodontal regeneration with Emdogain
- Limited evidence for periodontal regeneration with membranes
- Limited evidence for routine implant surgery

Therapy

- Necrotising Ulcerative Gingivitis (NUG)
- Periodontal abscess
- Periodontitis????

- **May be useful in:**
  - Localised/Generalised Aggressive periodontitis
  - Refractory disease

- **Greatest improvements in sites >6mm**

- **Minimal benefit in chronic periodontitis**
  - Responds well with conventional periodontal therapy

3. Antibiotics used as an adjunct, not replacement in periodontal therapy

- **Subgingival plaque biofilm**
  - Diverse microbial community
  - Exists outside of host
  - Barrier to diffusion
  - Increased antibiotic resistance
- **High gingival crevicular fluid (GCF) levels required for biofilm penetration**
- **Systemic antibiotics alone**
  - GCF levels may not penetrate biofilm
  - Does not remove plaque retentive factors such as subgingival calculus

Current evidence suggests that the use of antibiotics alone are ineffective in the treatment of periodontitis

- Adjunct to subgingival debridement
  - Immediately after initial phase
  - At re-evaluation phase
- Quality of subgingival debridement affects treatment outcome
- Poorer outcome when performed by students or less experienced clinicians

4. Different agents for different situations

- Tetracyclines
- Metronidazole
- Amoxicillin/Metronidazole
- Azithromycin

- Important therapeutic considerations
  -Medical status and concomitant medications
  -Likely microbial species
  -Lack an easy to use, cost effective microbiological test
  -Not all aetiological species identified
  -Limited antibiotic agents available
  -Most regimens remain largely empirical
  -Limited evidence for optimal dosage and duration

Refractory Periodontitis

- Polymicrobial (A.a, P.g, T.f, P.i, Strep.)
- Considerations
  - Number of unresponsive sites
  - Host response
  - Presence of modifying factors
  - Extended antibiotic duration in smokers
- Metronidazole (Obligate anaerobes,A.a,gram –ve)
  - 200-400mg tds 5-7 days or
  - Amoxicillin-clavulanate potassium
  - 375mg:250mg-125mg tds 14 days or
- Azithromycin
  - 500mg once daily 3 days
  - Limited evidence
  - Benefit in deep sites and smokers

Aggressive Periodontitis (Grade C)

Localised Aggressive(molar incisor pattern)

- A.a implicated
- <u>Tetracyclines</u>
  - Tetracycline HCl 250mg qds 14 days
- A.a not suppressed at all sites
  - Resistance
  - Variable GCF concentration

Generalised Aggressive

- Polymicrobial

  (P.g, T.f +/- A.a)
- <u>Tetracyclines</u>
  - Limited or no effect

Aggressive Periodontitis

Localised Aggressive (molar incisor pattern)	Generalised Aggressive

- **Amoxicillin/Metronidazole**
  - 250-500mg/200-400mg tds 5 days

    or

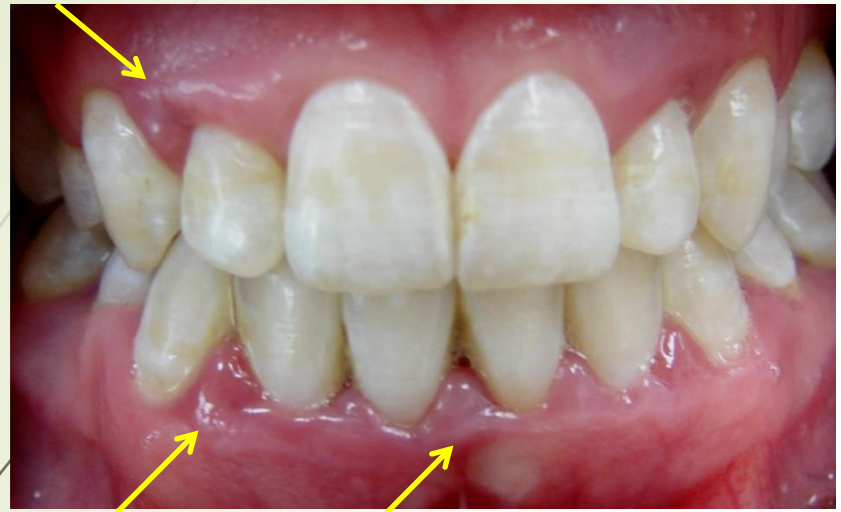
- **Azithromycin**
  - 500mg once daily 3 days
  - Early evidence promising

Azithromycin

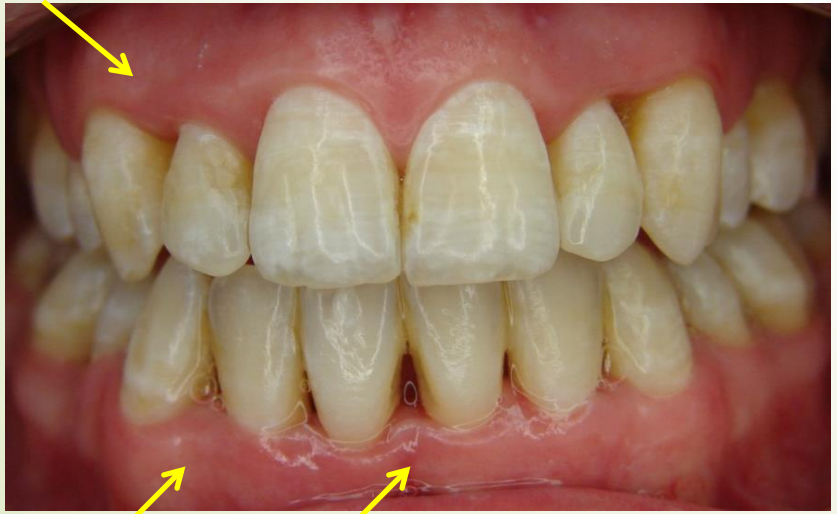
- Macrolide
- Few adverse effects
- Wide antimicrobial spectrum
  - Aerobic and anaerobic bacteria
  - Effective against A.actinomycetemcomitans and P.gingivalis
- High periodontal tissue concentrations for 5 days after administration
- Improved patient compliance

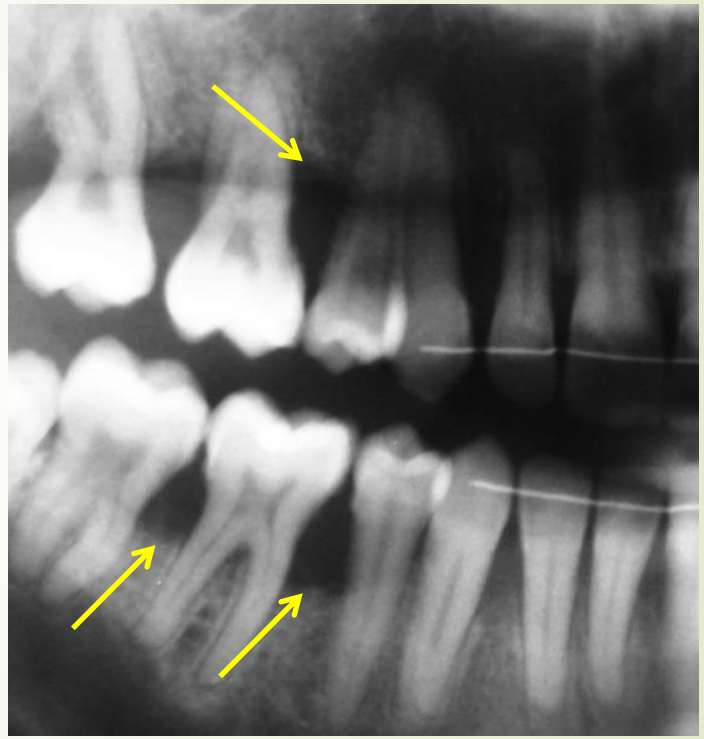
Generalised Aggressive Periodontitis(Grade C)

Baseline



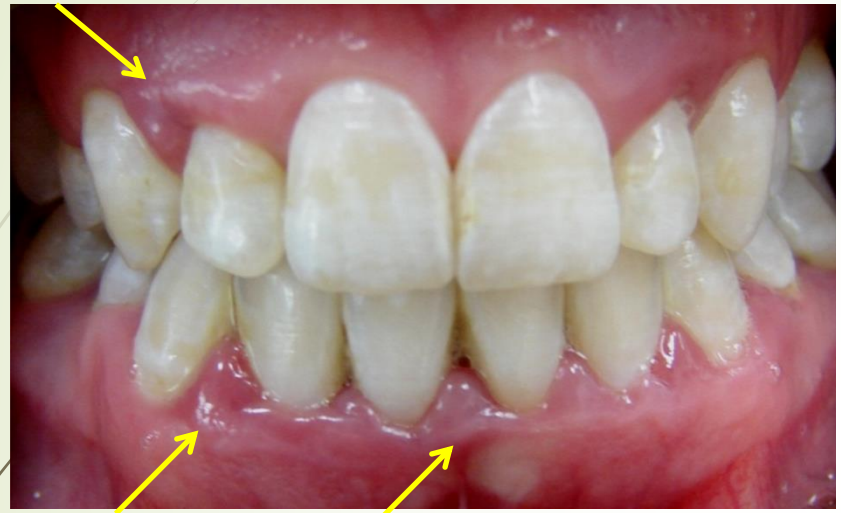
5 months post treatment





Generalised Aggressive Periodontitis(Grade C)

Baseline



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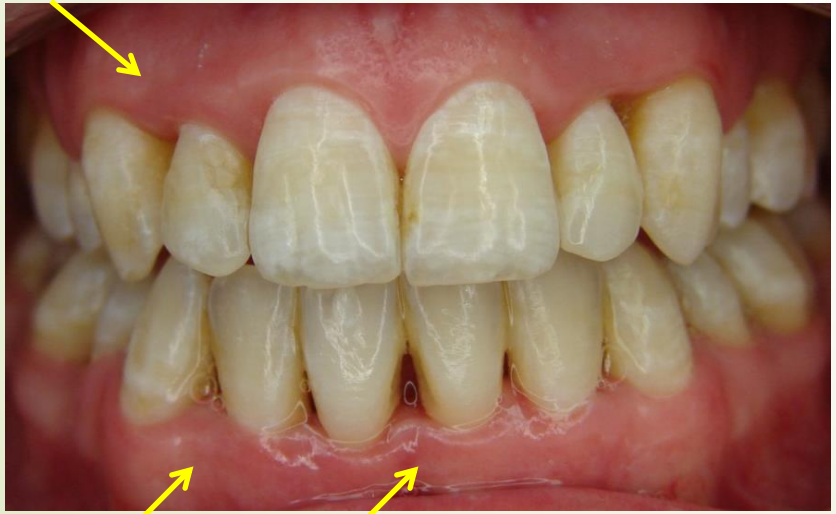
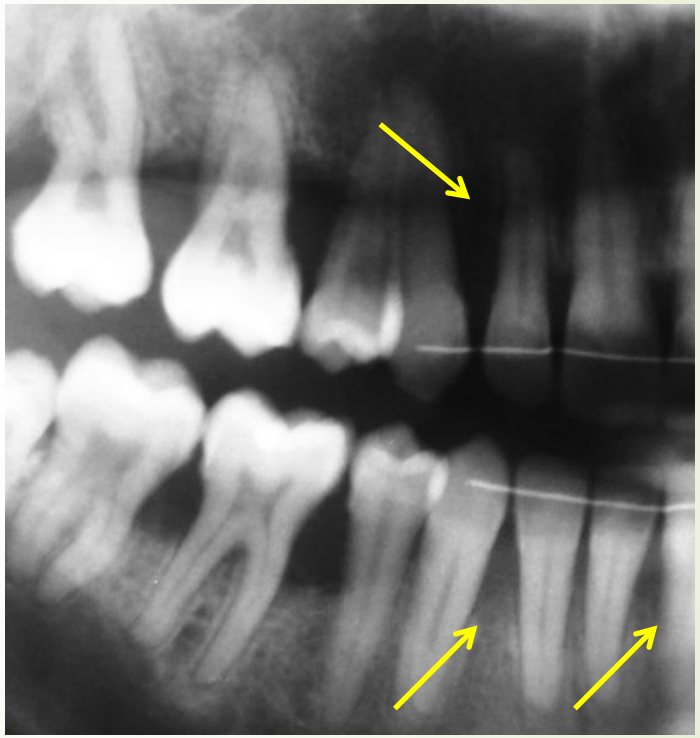
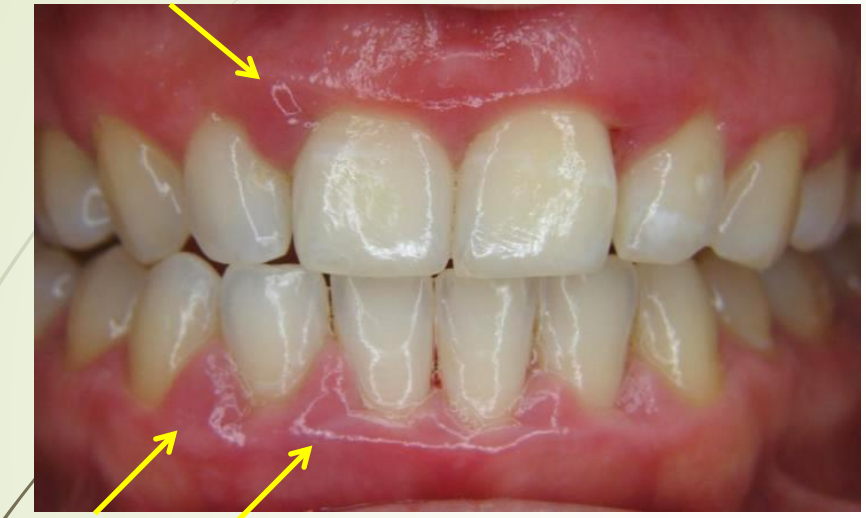
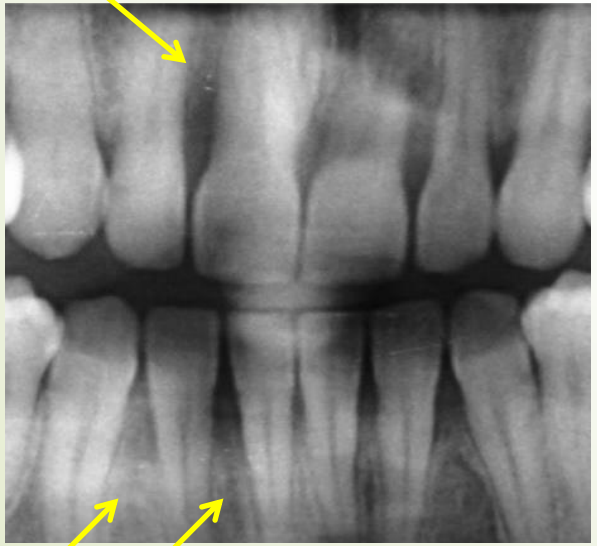




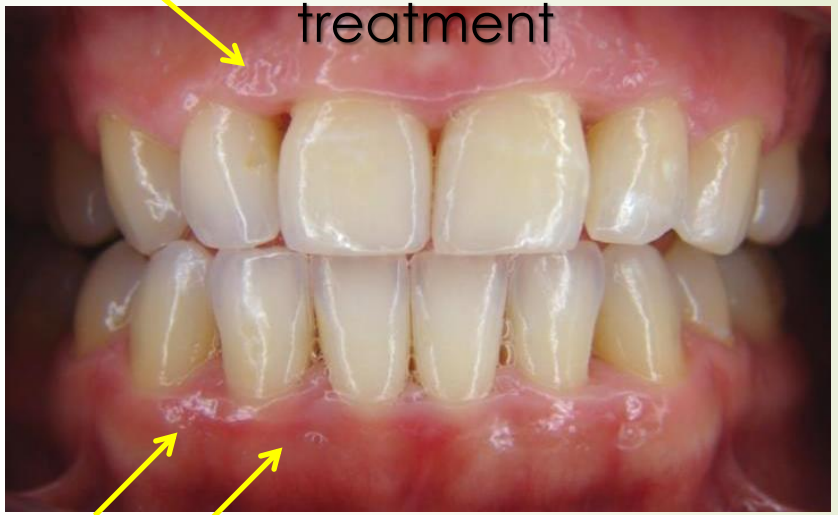
Localised Aggressive Periodontitis(molar incisor pattern)

Baseline

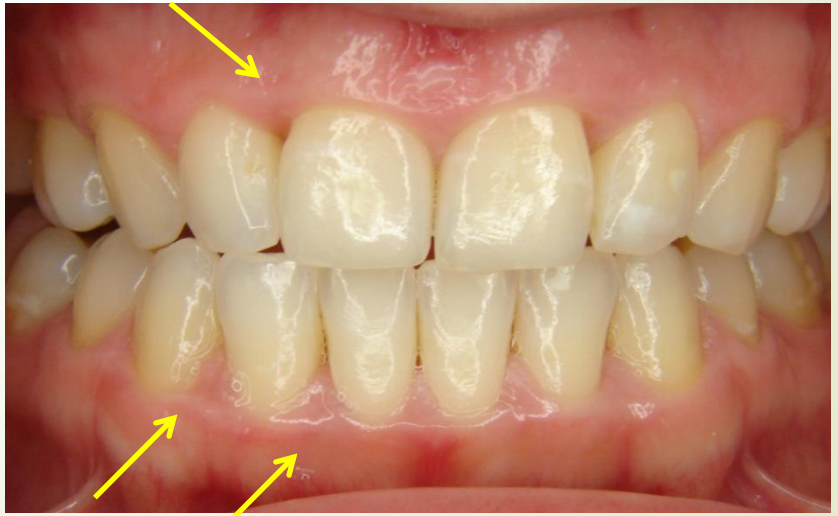




3 months post treatment



13 months post treatment



5. Antibiotics can result in re infection/recolonisation

- A.a, P.g, T.f, T.d
- Recolonisation
  - Supra and subgingival plaque
  - Mucous membranes, tongue, tonsils
- Regular biofilm disruption required during SPT

Conclusions

- Antibiotics are valuable therapeutic agents
- Not magic bullets
- Widespread use – bacterial resistance
- Clinicians need to be responsible for sensible prescribing
- Limited clinical scenarios
- Not an excuse for poor surgical technique
- Risks of complications may be greater than the risk of postoperative infection occurring
- Risk small at a patient level but significant risk at population level for preventable adverse events
- Diagnosis important

- Not an excuse for inadequate debridement
- Adjunct to reduce level/composition of bacteria to one compatible with host
- Importance of host response and modifying factors
- Most regimens largely empirical
- Further studies required to provide guidelines

Antibiotic & Antiseptic Use in Periodontal Therapy Part 2

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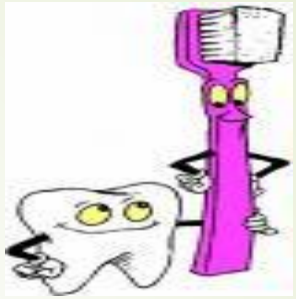
Chemical Plaque Control- Mouthrinses

Plaque control



- Toothbrushing
- When good oral hygiene is practiced, mechanical toothbrushing can remove plaque effectively
- Motivation tends to decline over time
- In industrialised countries, the average person brushes for less than one minute
- Combination of mechanical and chemical oral hygiene appear to offer some benefits

The concept of chemical plaque control

- The need to further improve plaque removal forms the basis of “chemical plaque control”
- Prevention of gingivitis is based on the assumption that gingivitis is the precursor of periodontitis

So how often does gingivitis progress to periodontitis?

- Poor predictor for future periodontitis
- The proportion of gingival lesions that convert to periodontitis is currently unknown
- The factors that cause the conversion are not well understood
- The most convincing evidence that gingivitis do not progress to periodontitis comes from epidemiological studies on untreated populations in China, Kenya, and Nigeria.

Chemical plaque control agents: First, second, third generation

1. **First-generation:** do not exhibit any significant substantivity (only minutes), can kill bacteria on contact, but have limited abilities to exert an effect on the oral flora after expectoration (e.g. cetylpyridinium chloride and sanguinarine)
2. **Second-generation** antimicrobial agents: high substantivity (hours), have an immediate antibacterial effect and more importantly, have a prolonged effect on the oral flora (e.g. chlorhexidine).
3. **Third-generation:** moderate substantivity (hours), characterized by an ability to inhibit or disrupt the formation of plaque, no effect on bacteria. (The morpholinoethanol derivative-delmopinol)

- **Second-generation antimicrobial agents are still the agents of choice** (Consensus report 2nd European Workshop on Periodontology 1996)

Mouthrinse

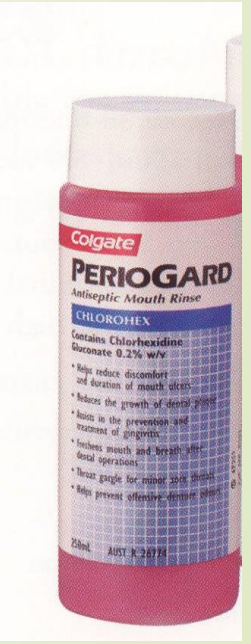
- Mouthrinses generally contain three basic ingredients:
- **Alcohol** - to enhance flavour impact and solubilize the flavour and some active ingredients; also acts as a preservative.
- **Surfactants -** dual function: to assist in the removal of debris from the mouth and provide antibacterial effects; aid in solubilisation of flavour and some active ingredients.
- **Flavouring agents -** provide some breath-freshening properties.

Groups of agents used to control plaque and/or gingivitis

1. Bisbiguanide antiseptics
2. Quaternary ammonium compounds
3. Essential oils (EO)
4. Natural products
5. Oxygenating agents
6. Amine alcohols
7. Enzymes
8. Others

Chlorhexidine (CHX)

- Bisbiguanide antiseptics
- CHX is the most studied and effective antiseptic in this category
- Developed in the 1940s in England
- Cationic(+ charge) antiseptic
- Broad spectrum antimicrobial
- After 20 years of use by the dental profession, CHX is recognized as the **GOLD** standard against which other antiplaque and gingivitis agents are measured



The mechanism of CHX effect

- Chx is a mouth rinse in a water base or alcohol base; contains glycerine, flavouring agents. Available in a gel form.
- It is a positively charged compound and thus attracted to negatively charged bacterial cell wall – breaks down cell wall & causes cell death
- It is adsorbed to plaque, pellicle, the oral mucosa, hydroxyapatite; and these surfaces become reservoirs - slowly release active Chx for up to 12 - 24 hours --- "substantivity"
- Any bacteria adhering to the tooth surface are either killed (bactericidal effect) or are prevented from multiplying (bacteriostatic effect)
- The persistent, bacteriostatic effect of CHX is what makes CHX the gold standard
- It has anti-plaque (reduces by 45-61%) and anti-microbial activity (reduces gingivitis by 27-67%) which is very effective

Optimizing the use of chlorhexidine

- **CHX should not be used before, or immediately after using toothpaste**
  (or else it will reduce the effective delivery of CHX to the tooth surface in an active form)
- **Limit intake of foods and beverages during treatment with CHX, especially just after use of CHX**

Quaternary ammonium compounds

- Cetylpyridinium chloride (CPC)
- CPC mouthrinses have been marketed in the USA since 1940
- Cationic in nature.
- CPC is used in a wide range of antiseptic mouthrinses
- CPC has a broad spectrum antimicrobial activity
- Substantivity is less than CHX ~ 3 hours (Roberts & Addy 1981)
- Little evidence of any benefits to improve gingivitis

Side effects of CPC

- **CPC shares some of its side effects as CHX:**
- Tooth staining
- Calculus formation
- Burning sensation

Essential oils (EO)

- Approved in 1987 in USA
- Contain 2 phenol-related essential oils:

  Thymol

  Eucalyptol

How does Listerine work?

- Microorganisms are killed by disrupting their cell walls and by inhibiting their enzyme activity
- Prevents bacteria from aggregating, and slows bacterial proliferation
- Reduces bacterial load
- A recent systematic review on essential oils concluded "When used as an adjunct to unsupervised oral hygiene, EO provides an additional benefit with regard to plaque and gingivitis reduction as compared to a placebo or control mouthrinse"
- Some studies suggest as an alternative to CHX (Pizzo *et al.* 2008)
- Compared to CHX, efficacy of Listerine is inferior (Paraskevas 2005; Stoeken *et al*. 2007)

Safety of Listerine

- Long-term use safe (Walker et al. 1989)
- Concern has been raised about the association of long-term use of a high-percentage alcohol-content mouthrinse with oral cancer (Elmore & Horwitz 1995)
- No evidence of cancer (Cole *et al.* 2003; Winn *et al.* 2001; Carretero Pelaez *et al.* 2004)
- Currently Listerine without alcohol is present in the market
- Possibility of producing pathological change should be borne in mind when considering long-term use of a mouthwash over a lifetime (Paraskevas 2005)

Triclosan

- Triclosan - trichloro-2-hydroxydiphenyl ether – is an antibacterial agent

  - usually incorporated with copolymer of polyvinyl methyl ether maleic acid (PVM/MA)

- The copolymer helps to retain the triclosan on the hard and soft tissues allowing for better anti-plaque activity and substantivity (long acting) .

Triclosan

- triclosan and copolymer
- eg Colgate Plax,
- Colgate Total toothpaste;

- can help to reduce

supragingival plaque/calculus & gingivitis (not as effective as CHx)

- Forbidden in 2016 by FDA in soaps

Natural products

- Herb and plant products have been used for many years if not centuries
- The blood root plant Sanguinaria canadensis provides an alkaloid extract called “sanguinarine”
- The product is incorporated in mouthrinse formulations & with zinc chloride (salts) to enhance the anti-plaque effect (which makes it difficult to evaluate the efficacy of sanguinarine alone)
- It may cause leukoplakia.
- **Limited benefit** (even when combined with zinc) (Quirynen *et al.* 1990)

Oxygenating agents

- H_2O_2
- Most commonly used in cases of ANUG and pericoronitis
- Limited evidence available to suggest use as an antigingivitis or antiplaque agent

Amine alcohols

- Considerable promise as antiplaque agents
- Octapinol was first studied, withdrawn for toxicologic reasons
- Delmopinol followed at 0.1% and 0.2% concentrations in mouthwashes. It does not kill the bacteria but disrupts the plaque matrix
- Many side effects have been reported: tooth discolouration; transient numbness of the mucosa such as the tongue; taste disturbance; and burning sensations in the mouth
- When compared to CHX, effectiveness was below CHX (Lang et al. 1998)

Enzymes

Biotene,Zendium – mouth rinse

- marketed for people with sensitive mouths/dry mouths
- no alcohol
- natural enzymes that are found in saliva – replenish and also have antibacterial effect
- Glucose oxidase; Lactoperoxidase; Lysozyme;Lactoferrin

Other antiseptics

- Many other agents have been studied but most have been found to have little or no effect clinically
- Povidone iodine: at 1% has a substantivity of only 1 hour (Addy & Wright 1978); minimal plaque inhibitory activity (Addy *et al.* 1977) ; or action in acute infections (Addy & Llewelyn 1978)
- As a rinse, has potential to affect thyroid function (Wray *et al.* 1977)

Can mouthrinses treat periodontitis??

- The use of mouthrinses is increasing, especially as adjuncts to the daily mechanical oral hygiene (Netuschil, 2003)
- "Mouthrinsing failed to achieve any significant penetration of pockets" (Pitcher *et al.* 1980)
- The lack of penetration may have been due to the presence of subgingival calculus or of a band of tightly adapted pocket epithelium immediately coronal to the epithelial attachment (Newman 1976)
- Conclusion that mouthwash does not affect subgingival plaque (Flötra *et al.* 1972)

Indications for use of mouthrinse as an adjunct

- After surgical procedures
- In medically compromised patients: those receiving chemotherapy or radiotherapy and bone marrow transplant patients

Conclusion

- CHX is the GOLD standard for mouthrinse
- CHX mouthwash does not affect subgingival plaque due to the lack of subgingival penetration
- Limited use in treatment of periodontitis
- Chemical plaque biofilm control has been shown to be effective for both plaque biofilm reduction and improved wound healing after periodontal surgery. Both chlorhexidine and essential oil mouthrinses have significant positive effects when prescribed for use after periodontal surgery for 1 to 4 weeks.

Mouthrinses have a role in gingivitis prevention, but considering gingivitis does not necessarily progress to periodontitis, we need to question whether the use of chemical agents for the general population is really necessary

Many research studies and clinical trials to find ideal chemical anti-plaque/ antibacterial agent

- very difficult task
- new products constantly tested
- need to be aware of what's on the market

Before advising on a product :

- do your own research of the literature
- Scrutinise the product labels
- Provide clear instructions to the patient
- Be aware of shelf life