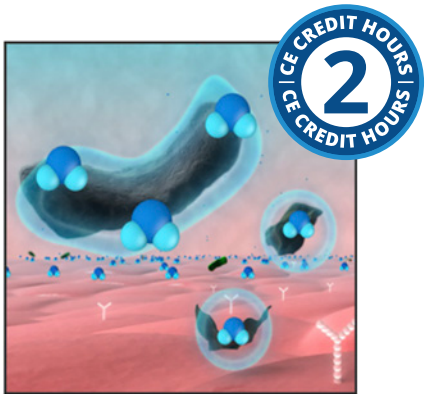
# Re-examining the Plaque-Gingivitis Connection and the Role of Stannous Fluoride

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## Conflict of Interest Disclosure Statement

- The authors have done consulting work for Procter & Gamble. They have no relevant financial relationships to disclose.

## Introduction – The Plaque-Gingivitis Connection

The purpose of this course is to review the role of plaque in the initiation of periodontal disease, share novel insights on the mechanism by which stannous fluoride reduces plaque-induced gingivitis, and discuss practical implications for dental professionals.

## Course Contents



## Overview

Because gingivitis is highly prevalent and can progress to periodontitis in susceptible individuals, clinicians can recommend products containing antimicrobial agents as a means to inhibit bacterial metabolism and/or decrease bacterial quantity. Not all antimicrobials are equivalent. Recent research has shown another dimension by which the sole fluoride which is concurrently an antimicrobial – stannous fluoride – fights gingivitis: it reduces plaque toxicity via disruption of the normal inflammatory host response that would be triggered by the presence of plaque endotoxins in the gingival sulcus. Using a well-formulated antimicrobial bioavailable fluoride toothpaste is an easy to adapt and research-supported means for: 1) gingivitis prevention in healthy but susceptible patients; and 2) chemotherapeutic treatment for patients with existing disease.

## Learning Objectives

**Upon completion of this course, the dental professional should be able to:**

- Explain the risk factors associated with gingivitis, including the contribution of plaque quantity and host susceptibility.
- Identify common chemotherapeutic oral antimicrobials and their respective benefits, and describe how stannous fluoride is distinct in its modes of action in gingivitis reduction.
- Define the mechanism by which stannous fluoride interacts with plaque bacterial endotoxins to reduce the inflammatory response.
- Discuss the implications of bioavailable stannous fluoride use for patient care.

## Introduction

Emily is a 33-year old patient who reports brushing her teeth every day after breakfast and before bedtime, and flossing twice a week. She presents with minimal plaque at her biannual preventive care appointments, suggesting her oral hygiene self-assessment is probably accurate. Yet, Emily states that her gums often bleed, and the exam reveals marginal redness, edema, and widespread bleeding upon probing, as shown in the representative example in Figure 1. There is nothing in her medical history or concomitant medication use that appears contributory. How can the apparent disconnect between Emily's home care skills and her clinical status be explained if the quantity of residual plaque is the sole determinant in gingivitis and its extent? Is Emily a rare case?

Emily's situation stands in stark contrast to that of Daniel, a 42-year old patient who generally comes to his appointments with moderate to heavy supragingival plaque. He admits that oral

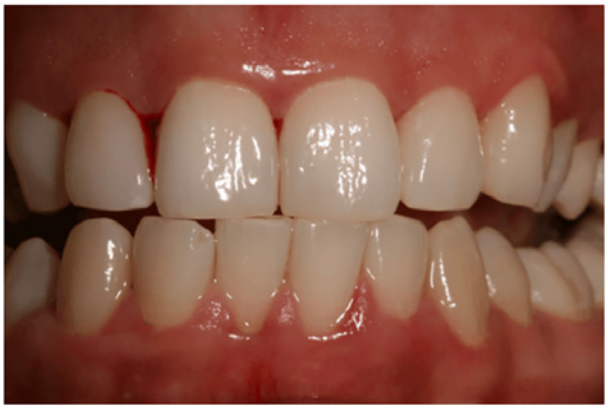

**Figure 1.** Gingival bleeding and areas of inflammation are present despite little plaque accumulation in this patient example.

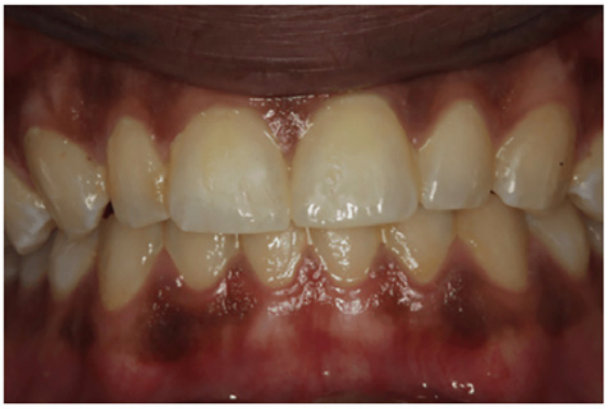

**Figure 2.** A representative depiction of the gingiva of a patient who – despite subpar oral hygiene and visible plaque – doesn't show overt gingivitis symptoms.

hygiene is not a top priority, while nonetheless displays few signs of gingivitis and no pockets (Figure 2 illustrates this hypothetical case). Is he, too, an anomaly?

## Plaque Quantity: Determinant of Gingivitis Severity?

The cause-and-effect role of undisturbed, proliferating pathogenic plaque in initiating the classic signs of gingivitis is well-established, as is the correlation between plaque removal and a corresponding improvement in gingival bleeding and inflammation.[1-4] Yet clinical research scientists observed a perplexing outcome in review of investigations of a bioavailable stannous fluoride ($SnF_2$) dentifrice: the magnitude of the overall gingivitis reduction benefit following regular $SnF_2$ use was typically much larger than the magnitude of the mean plaque reduction benefit.[5-7] Table 1 shows results from three 6-month clinical studies comparing bioavailable $SnF_2$ dentifrice with a negative control that included both plaque and gingivitis evaluations. Six-month data revealed that $SnF_2$ users averaged 17-22% less gingivitis and 33-57% less gingival bleeding, but only 3-8% less plaque compared with the negative control.

What might explain this disproportionate gingivitis-to-plaque reduction benefit ratio? If lowered plaque mass did not appear to align with the reduction in gingivitis on a parallel basis, what accounted for the strikingly greater relative decrease in gingival inflammation and bleeding? These intriguing results spurred new inquiry and research and led to recent findings revealing the actions of $SnF_2$ in reducing plaque toxicity below the gumline and heading off an inflammatory cascade. Brushing with bioavailable $SnF_2$ dentifrice provides gingivitis-fighting efficacy that goes beyond plaque quantity reduction; the reduction in subgingival plaque toxicity mechanisms appear to augment $SnF_2$'s well-established sustained bactericidal/bacteriostatic and acid suppression actions to produce significant gingivitis improvements.

In considering Emily and Daniel, it is now known that the quantity of undisturbed plaque is not necessarily always a clear predictor of the

**Table 1. Comparison of Gingivitis and Plaque Quantity Reduction Benefits with Bioavailable Stannous Fluoride Reference.**

| | Gingivitis Reduction Benefit | Bleeding Reduction Benefit | Plaque Reduction Benefit |
|---|---|---|---|
| McClanahan *et al., J Clin Dent,* 1997[5] | 20.5% | 33.4% | 3.1%* |
| Mankodi *et al., J Clin Periodontol,* 2005[6] | 21.7% | 57.1% | 6.9% |
| Mallatt et al. J Clin Periodontol, 2007[7] | 16.9% | 40.8% | 8.5% |

*p>0.05. All other values p<0.05.

gingival health status and degree of bleeding for any given patient. Instead, while some patients like Daniel can seemingly maintain relative gingival health (at least initially) despite subpar oral hygiene, another subset of patients like Emily may struggle to stave off gingivitis even when oral hygiene is good.

A new body of evidence around gingivitis/periodontitis causality has emerged in recent years that suggests certain individuals seem to have an increased susceptibility to developing gingivitis irrespective of their plaque removal efforts, and/or are more likely to see their gingivitis evolve into the early stages of periodontal disease than others with comparable plaque levels and plaque bacterial composition.[8,9]

Multiple published reports on this population variability suggest that the influence of an individual's genetic factors and host response play a significant role in the gingival inflammatory response to plaque pathogenicity and the development and progression of disease for some.[8-12] In-office patient profiling of genetic gingivitis susceptibility is not currently a reality, but the knowledge that a subset of patients may have an exaggerated response to even small quantities of plaque has important implications for prevention and treatment that go beyond routine mechanical oral hygiene, especially in light of very notable new findings about the anti-inflammatory properties of a mainstay in oral antimicrobials: stannous fluoride.

## Inflammation and a New Pathway to Gingivitis Control

### Inflammation – The Big Picture

Before a discussion of the control of gingivitis, it is necessary to first grasp how inflammation occurs, and its relevance to disease in the periodontium. The word *inflammation* brings to mind imagery of 'angry-looking' tissue. Underlying and precipitating that surface manifestation lies a complex reactionary microcellular process that serves as a biologic defense operation to attack pathogenic microorganisms and other injurious or irritating stimuli. Within body systems, an external threat triggers the release of inflammatory mediators to attenuate or destroy it, and in the process causes characteristic signs of acute inflammation (e.g., heat, edema, erythema, exudate, pain).

The initial step in the inflammatory process involves threat **recognition**. Cells in bodily tissues functioning as 'look-outs' scan for probable irritants/injurious agents and detect that the invaders have unique patterns that differ from the host. This propels the **recruitment** phase of inflammation, where host inflammatory mediators like cytokines are mobilized, and bring about an immune response through vascular and cellular permeability effects.[13,14]

While inflammation has benefit as a protective and restorative healing mechanism in acute local reactions, when unresolved, inflammation can become chronic. Pro-inflammatory cytokines are implicated in the development pathways of serious systemic health conditions including Type 2 diabetes, cardiovascular disease, and adverse pregnancy outcomes.[15-17] These and other chronic inflammations – including oral health related – may result in irreversible damage unless there is intervention.

### How Gingival Inflammation Develops

Supragingival plaque is initially colonized primarily by gram positive aerobic bacteria; e.g., Streptococcus, Haemophilus, and Neisseria species (Figure 3).[18] If plaque deposits are left undisturbed and allowed to mature, the subgingival microbiota composition shifts to predominately gram-negative anaerobic bacteria and becomes more virulent. Examples of frequently found subgingival plaque bacterial species include *Aggregatibacter actinomycetemcomitans, Tannerella forsythia, Porphyromonas gingivalis, Campylobacter rectus, Prevotella intermedia*, and *Selenomonas* species.[18-21]

What, specifically, does the corresponding inflammatory process look like in the gingival tissues? In the very earliest stage where plaque and/or calculus are serving as an irritant in the sulcus (initial lesion), only histological tissue changes can be seen.

If homeostasis is not restored by modulation or removal of the irritant, this lesion will likely become pathologic (early lesion) and lead to visible local vasodilation, edema, and increased gingival crevicular fluid.[22,23]

A well-orchestrated intracellular signaling pathway governs the pathogen/host tissue interface. **Toll-like receptors (TLR)** in the periodontium, predominately 'TLR4' and 'TLR2', reside on the cell walls in the periodontal ligament fibroblasts, the gingival fibroblasts, the epithelia, the endothelia, and also in the cells of an individual's immune system, including macrophages and neutrophils. During the recognition phase, TLRs scan for bacterial pathogens like those residing in the biofilm of plaque, and then mount a complex defense reaction if provoked.[23-29]

A closer look at the inflammatory defense reaction shows that TLR bind and interact with plaque bacterial endotoxins, such as lipopolysaccharides (LPS) and lipoteichoic acid (LTA). This interaction induces a series of events which includes the production of inflammatory-generating cytokines (e.g., interleukin-1beta, interleukin-6) and other effector molecules. Toxic metabolites produced by the invading pathogens further provoke and increase the TLR response and can result in reduced tissue repair, more inflammation, and greater permeability of the tissue (Figure 4).[23-29]

Should the early lesion progress to an established lesion with a proliferation of plasma cells, lymphocytes and macrophages, moderate-severe gingivitis will be apparent with clearly visible gingival contour, color, and bleeding abnormalities (Figure 5).

In susceptible patients – and without intervention and a return to homeostasis – there is ultimately a transition to an advanced lesion. Chronic inflammation results, which may lead to extracellular matrix tissue destruction and possible bone loss associated with periodontitis.[22,23]

## Stannous Fluoride as a Plaque Toxicity Modulator

If mechanical plaque removal is not universally well-practiced, and certain patients – even with decent oral hygiene – react in an amplified fashion to plaque bacteria due to host susceptibility factors, what effective

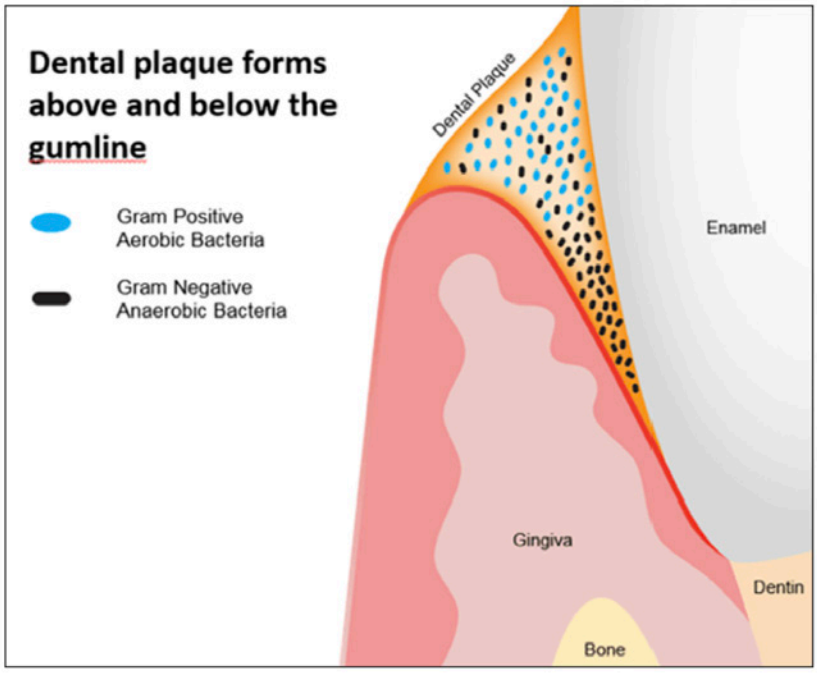


**Figure 3.** Dental plaque forms above the gumline and in the gingival sulcus. Bacterial composition varies with location; anaerobic bacteria predominate in the gingival sulcus.

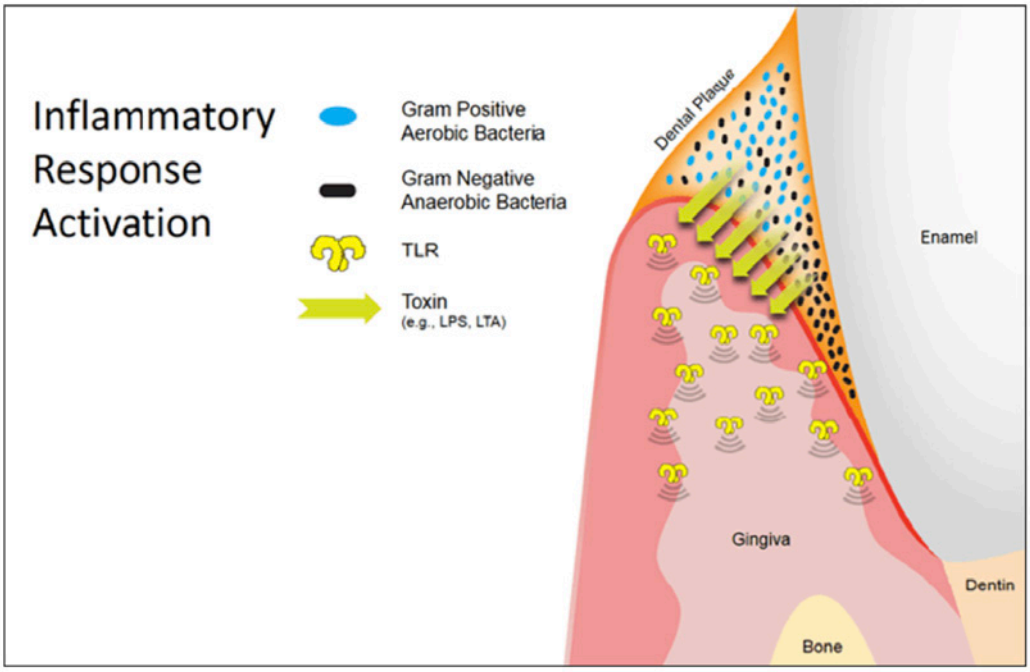


**Figure 4.** In the gingival sulcus, the unique patterns of plaque bacteria are recognized by host "look out" cells (TLRs), spurring interaction with them and their toxic metabolites and stimulating the recruitment of host inflammatory mediators to mount a defense. This leads to the classic clinical manifestations of gingivitis.

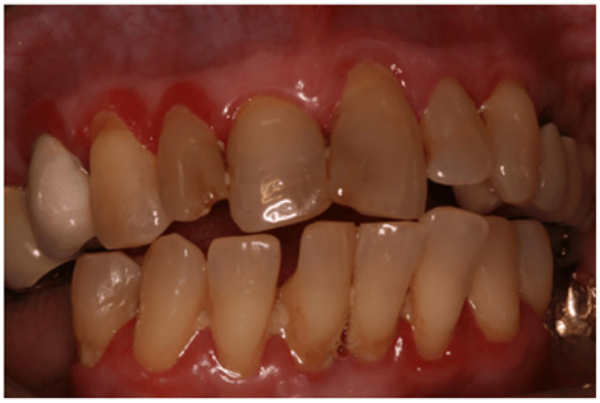

**Figure 5.** Recognizable signs of established gingivitis include red, edematous, bleeding gums.

solutions exist for the prevention and control of gingivitis? Adjunctive, commercially available chemotherapeutics like bioavailable stannous fluoride $SnF_2$ dentifrice that can impact plaque toxicity irrespective of plaque quantity are an intelligent strategy in light of nearly ubiquitous usage of toothbrushing as the main oral hygiene practice.

Why focus on this particular antimicrobial? There are several reasons why $SnF_2$ has a distinct profile among oral chemotherapeutics options:

- Of the three fluorides most commonly incorporated in commercial toothpastes today, stannous fluoride ($SnF_2$) is the sole anti-caries agent that is also an antimicrobial agent, providing clinically proven benefits against plaque, gingivitis, and breath malodor.
- The bacteriostatic/bactericidal effects of $SnF_2$ are sustained beyond the brushing window due to its notable substantivity (i.e., ability to be retained in the oral cavity after exposure).[30,31]
- $SnF_2$ is also the only common fluoride source to protect against both enamel erosion and dentinal hypersensitivity.[32-35]

Bioavailable $SnF_2$ 's gingival health properties are well-established and recognized to be associated with its anti-plaque effects, such as inhibiting and reducing plaque bacteria's adhesion and growth, along with the inhibition of acid production and other metabolic toxins[30,31,35] However, research has shown that the quantity of plaque bacteria does not firmly correlate with gingival inflammation.[24] To explore if other factors beyond metabolic actions might be at play and whether $SnF_2$

could directly interact with bacterial endotoxins to affect pathogenicity, a series of laboratory and clinical investigations employing novel methodologies were conducted to evaluate the potential plaque endotoxin binding to oral care cationic antimicrobials like $SnF_2$ [25-27,37-41] This research generated the findings highlighted in this course revealing an additional means by which bioavailable $SnF_2$ apparently acts to control plaque while preventing and reducing gingivitis: $SnF_2$ disrupts the gingival inflammation process by reducing plaque toxicity.

A summary of the studies' findings on this effect showed that before the host TLRs in the gingival sulcus can mount the inflammatory response that would be expected when encountering plaque bacteria endotoxins, $SnF_2$ present in the mouth (e.g., from toothbrushing) intervenes and binds the endotoxins, thus effectively blocking them from affixing with TLRs, and undermining the typical cytokine-driven series of events that leads to inflammation and bleeding (Figure 6).

With regular exposure to a properly formulated bioavailable $SnF_2$ dentifrice, then, the customary deleterious effects of plaque endotoxins can be blunted, preventing gingivitis or reducing it to a level consistent with homeostasis, and lowering the potential for more advanced periodontal disease.[25-27] Click on Figure 7 to view an animation illustrating this process.

To better visualize how bioavailable fluoride impacts the inflammatory response, consider the example of a traditional alarm clock (Figure 8). Here the electrical cord connecting the alarm clock to the electrical outlet symbolizes host TLR, while the outlet is analogous to plaque LPS endotoxin. In the absence of $SnF_2$, plugging in the cord (TLR) to the outlet (LPS) results in a preset alarm functioning by going off – or in the case of TLR/LPS – the triggering of the inflammatory cascade.

However, if a childproof outlet protector covers the electrical outlet and blocks the cord from being plugged in (see the bottom/lower outlet in Figure 8) the clock has no power and the alarm cannot be activated. Similarly, with bioavailable $SnF_2$ acting in like fashion to the safety outlet cover, LPS is bound and the gingival inflammatory response is thwarted.

## Clinical Testing is Congruent with *In Vitro* Findings

Controlled *in vivo* trials are an important means of confirming the validity and application of laboratory testing. Randomized controlled clinical trials with additional toxicity measurements have confirmed these effects.

Research by Klukowska and colleagues incorporated subgingival plaque sampling in sites up to 4 mm in depth in a 4-week randomized controlled clinical trial of twice

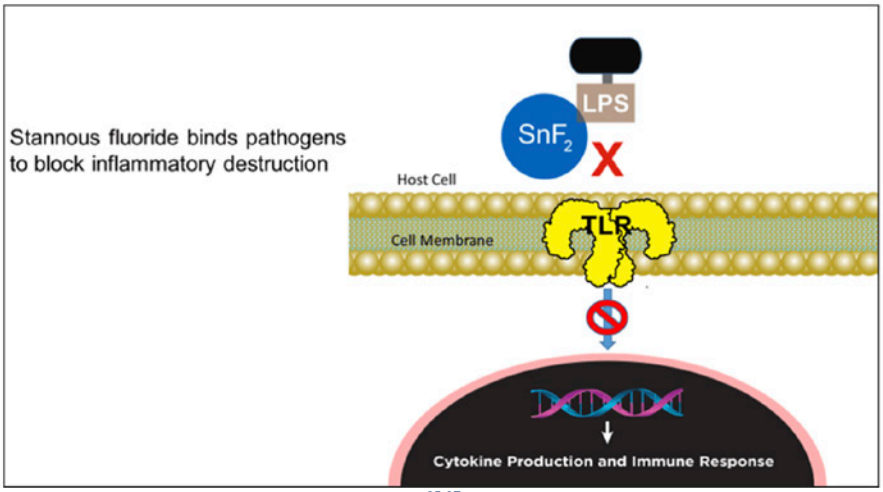


**Figure 6.** In laboratory investigations,[25-27] bioavailable stannous fluoride blocked the reactivity of plaque endotoxins (e.g., LPS) to toll-like receptors (TLR) to effectively diffuse the host cytokine-driven inflammatory response.


**Figure 7.** Video illustrating stannous fluoride's ability to bind to endotoxins, thereby preventing the activation of toll-like receptors and the inflammatory response. *Click on image to view video online.*

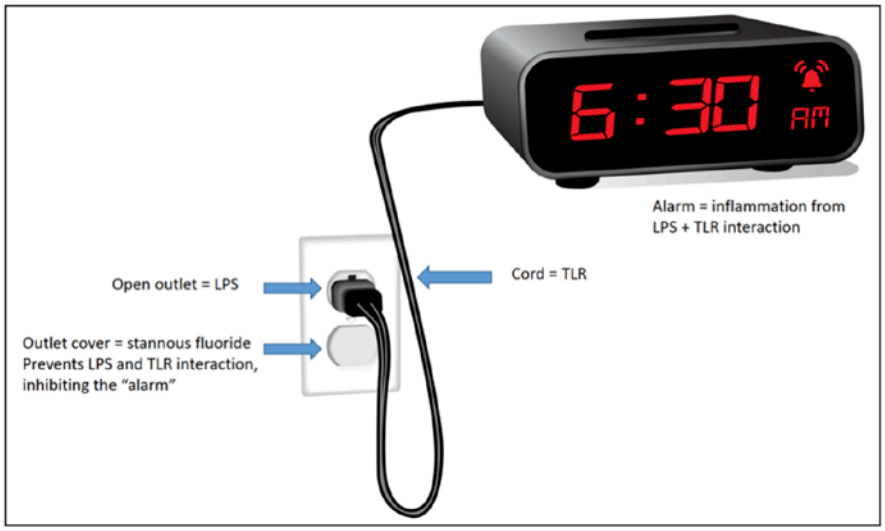


**Figure 8.** Host toll receptors can be imagined as the electrical cord that plugs into the outlet (i.e., LPS) and incite the inflammatory cascade (here the alarm sounding) in the absence of stannous fluoride.

daily unsupervised brushing with a 0.454% bioavailable $SnF_2$ dentifrice, wherein both a low gingival bleeding cohort ('healthy') and a high bleeding cohort ('diseased') were evaluated.[36] Clinical effectiveness trials of marketed dentifrices do not commonly include subgingival plaque sampling, but its inclusion in this trial provided insight into the depths of penetration of $SnF_2$, its retention, and its ability to reduce subgingival plaque toxicity.

At Week 4, both cohorts saw significant (42% to 53%) mean reductions in gingival bleeding. The plaque sampling results in both the healthy and diseased groups provided evidence following use of $SnF_2$ of notably decreased LPS/LTA dye activity and TLR activity. Morning wake-up plaque samples via salivary lavage showed significantly suppressed short-chain carboxylic acid toxins for both the low and high bleeding groups as well, suggesting robust

substantivity.[37,38] By measuring the endotoxin content of the subgingival plaque samples via dye assays and plaque isolates activated gene expression in the TLR reporter cell lines, it was concluded that "SnF2 dentifrice treatment was associated with broad scale reductions in endotoxin content and virulence potentiation properties of dental plaque samples collected subgingivally from patients."[39]

The researchers noted the important implication of this research and a previous complementary trial:[40] The effects of $SnF_2$ to bind with endotoxins and thereby limit TLR4/TLR2 in initiating the inflammatory cascade manifested both in the diseased, high bleeding sites and also in the low bleeding sites with minimal measurable disease, suggesting a preventive as well as a treatment gingivitis strategy.

A subsequent clinical trial evaluating $SnF_2$ penetration within the sulcus and retention in gingival crevicular fluid (GCF) provided further evidence that $SnF_2$ can influence the pathogenicity of microflora subgingivally.[41] In this 2-week trial of subjects with a minimum of twenty bleeding dental pockets up to 4mm in depth and no recent $SnF_2$ exposure, GCF samples were analyzed by mass spectrometry for the presence of tin (a stannous fluoride marker) at both 30 minutes and 12 hours after brushing with a bioavailable $SnF_2$ dentifrice on Day 1. The results showed that significant (P<0.0001) levels of tin compared with baseline were detected in the GCF samples. Higher tin levels were seen at Day 14 after 2 weeks of home dentifrice use, suggesting an incremental effect with ongoing use.

More confirmation of bioavailable $SnF_2$'s ability to diminish the virulence of subgingival plaque – and thus the development of gingivitis – was demonstrated by recent clinical research evaluating gingival inflammation and bleeding in 99 adult subjects with gingivitis.[42] After 8 weeks of at-home 0.454% $SnF_2$ dentifrice use, significant reductions in gingivitis and bleeding versus baseline were observed. These clinical observations were consistent with the results of subgingival plaque sampling, where TLR2 assay analyses of hTLR2 reporter gene activity showed significant (P=0.0004) mean reductions following two months of $SnF_2$ brushing (Figure 9).

Fine and colleagues evaluated the clinical effects on gingivitis and the oral microbiome of an SnF2 dentifrice stabilized with zinc phosphate in a controlled trial. Compared to a negative control, results showed significant improvement in bleeding on probing for SnF2 users, coupled with significant reductions in GCF levels of inflammatory markers and gram-negative bacteria.[43]

Incorporating $SnF_2$ in a dentifrice to yield maximum esthetics and efficacy – including

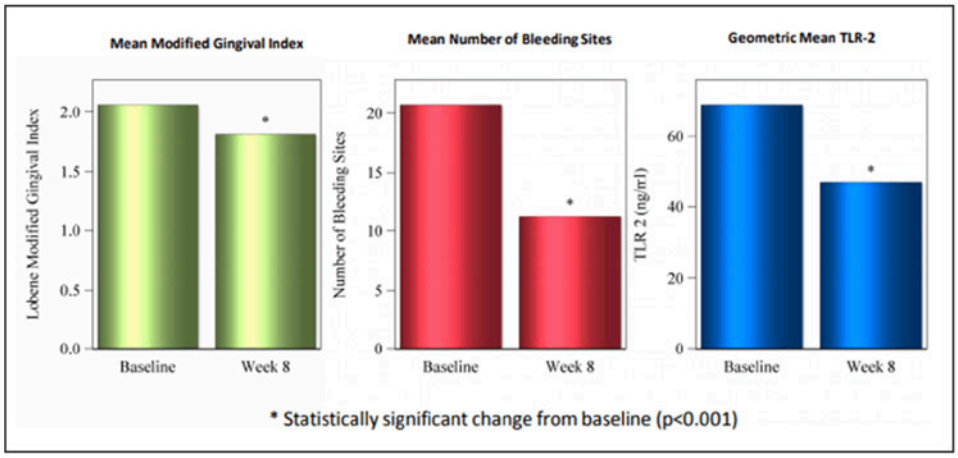


**Figure 9.** An 8-week clinical trial of 99 subjects with pre-existing disease showed significant reductions in bleeding and gingivitis with bioavailable $SnF_2$, consistent with significant reductions in hTLR2 reporter gene activity via subgingival plaque sampling.[39]

full bioavailability – mandates precise, well-skilled formulation.[44,45] In recent years, several technological advances resulting from ongoing scientific innovations and testing have led to bioavailable $SnF_2$ formulations which have provided superior tartar control and whitening benefits, along with the therapeutic benefits, versus a variety of dentifrice controls in multiple clinical trials. The extensive clinical research program by Procter & Gamble on $SnF_2$ dentifrice, which has spanned numerous decades, resulted in a Crest dentifrice being the first to be recognized for seven attributes applicable to toothpastes in the American Dental Association Seal of Acceptance program:[46]

- Prevent or reduce enamel erosion
- Prevent cavities
- Prevent and reduce plaque
- Prevent and reduce gingivitis
- Reduce tooth sensitivity
- Reduce bad breath
- Remove tooth surface stain.

The benefits have been demonstrated in clinical research. In one randomized clinical trial, the novel $SnF_2$ dentifrice demonstrated significantly greater plaque reduction than a negative control and significantly greater tin retention subgingivally than a positive control $SnF_2$ dentifrice.[47] In a separate 12-week clinical trial, the novel $SnF_2$ dentifrice produced statistically significant gingival bleeding reductions versus the negative control as quickly as after one week, demonstrating rapid activity. At Week 12, subjects using the $SnF_2$ dentifrice had 33.4% fewer bleeding sites and 6 times greater odds of transitioning from localized or generalized gingivitis (>10% bleeding sites) to generally healthy (<10% bleeding sites) versus the negative control.[48] A 2019 meta-analysis of 18 clinical trials evaluating the gingival health effects of bioavailable gluconate chelated $SnF_2$ dentifrices when used for < three months concluded that regardless of baseline level of disease, they significantly reduced gingival bleeding compared to positive and negative controls.[49]

## How can this New Knowledge Benefit Your Patients?

Since gingivitis is a highly prevalent condition[50] why is it that so many don't recognize it and/or take action when they encounter signs like overt bleeding during toothbrushing (*"My gums have always bled!"*), and aren't aware of the risks of ignoring gingivitis?[51,52] The role of dental professionals in addressing this disconnect is integral because they conduct and interpret clinical assessments that patients cannot, including:

- **Obtaining a thorough medical history** to determine any contributory role of underlying conditions or medications.[53-57]
- **Performing a visual examination** to assess the 'Three C's' of gingival presentation: Color, Consistency, and Contour.
- **Evaluating plaque accumulation**, including hard-to-reach areas that patients can't visualize.
- **Measuring periodontal pocket depths** to assess attachment loss. Concurrent bleeding on probing will be observable and can serve as an additional springboard to discuss gingivitis etiology and the fact that gingival bleeding is never normative.

It has been commonly presumed that there is a fairly predictable correlation between the age and/or the quantity (mass) of unremoved plaque and the severity of the corresponding gingival disease. Because of this, clinicians have typically taken the first-line approach for intervention by encouraging patients to reduce the amount of undisturbed plaque, namely through oral hygiene instruction in proper toothbrushing and flossing techniques and recommending more frequent preventive appointments.

A second (and often combined) professional strategy for addressing gingivitis beyond mechanical plaque control targets plaque regrowth through adjunctive antimicrobial chemotherapeutic products (e.g., dentifrices and mouthrinses) that can be incorporated into the patient's home care regimen. For example, optimally-formulated SnF2 dentifrices have been shown across studies to provide significant plaque inhibition effects versus controls on both brushed and unbrushed surfaces.[58] Cetylpyridinium chloride (CPC), chlorhexidine, and bioavailable $SnF_2$ are common oral chemotherapeutics in use today and prescribed or recommended to patients. Their respective modes of action, relative benefits, and notes of interest are outlined in Table 2.

**Table 2. Common Oral Chemotherapeutics.**

| Chemotherapeutic Oral Antimicrobial | Delivery Mode* | Method of Action(s) | Notes |
|---|---|---|---|
| Cetylpyridinium Chloride (CPC)<br><br>*[e.g., Crest® Pro Health Advanced Oral Rinse Multi-Protection,[a] Philips Sonicare Breath Rx,[b] CloSYS® Healthy Gums,[c] Therabreath™ Healthy Gums Oral Rinse[d]]* | Mouth rinse | Lysis of cell walls; inhibits/disrupts cell growth and metabolism.[59] | ✓ Proper formulation needed for maximum substantivity and bioavailability<br>✓ Published anti-plaque and anti-gingivitis efficacy[60-62]<br>✓ Patients must comply with an additional mouth rinse step |
| Chlorhexidine Gluconate (CHX)<br><br>*[e.g., Peridex™[c]; Periogard®[f]]* | Mouth rinse | Bactericidal; also inhibits glycosidic and proteolytic enzymes[63] | ✓ Prescription-only 0.12% rinse<br>✓ Well-established clinical plaque and gingival health benefits; a 'gold standard' for gingivitis treatment[64,65]<br>✓ Staining and taste often limit patient acceptance |
| Stannous Fluoride ($SnF_2$)<br><br>*[e.g., Crest® Gum Detoxify;[a] Parodontax;[g] Colgate® Total® Pro Gum Health;[f] Crest® Pro-Health paste,[a] Sensodyne Sensitivity & Gum;[g] Crest® Pro-Health Advanced Gum Restore[a]]* | Dentifrice | Bacteriostatic and bactericidal; substantive; blocks inflammatory precursors[25-27,30,31] | ✓ Only common anti-caries agent that is also antimicrobial<br>✓ Multiple studies show anti-plaque/gingivitis efficacy for a 0.454% $SnF_2$ bioavailable formula vs. various controls[6,7,36,45,66-70]<br>✓ Skilled formulation is critical for optimal bioavailability and esthetics |

[a]The Procter & Gamble Company [b]Philips Oral Healthcare [c]Rowpar Pharmaceuticals Inc. [d]Church & Dwight CO [e]3M Oral Care [f]Colgate Palmolive Company [g]Haleon

Patients are consumers who regularly encounter a plethora of product advertising through media in the drug store oral health aisle. When patients feel overwhelmed by all the choices, they rely on a trusted professional for product guidance. Evidence-based recommendations from published peer-reviewed research are paramount to help patients choose a well-tested and efficacious product with the best likelihood of addressing their particular needs. In the case of bioavailable $SnF_2$, there is a significant body of research supporting its use for a variety of indications, including plaque and gingivitis.[6,7,36,45,66-70] A systemic review by Johannsen and colleagues of 32 trials evaluating stabilized $SnF_2$ dentifrices concluded that "... stabilized $SnF_2$ toothpaste had a positive effect on the reduction of dental calculus build-up, dental plaque, gingivitis, stain and halitosis."[71]

## Adjunctive Oral Chemotherapeutics Leverage a Basic Truth

Realistically, very few individuals will attain the meticulous level of oral hygiene required to keep all gingival disease at bay.[72-75] Fortunately, however, nearly all patients own a toothbrush and toothpaste, so making a switch in dentifrice from a standard paste to a clinically-proven antimicrobial dentifrice is an easily adoptable, straightforward proposition with the potential for significant improvements in oral health.

Clinicians have an invaluable opportunity to enlighten their patients on the benefits of using antimicrobials. The International Federation of Dental Hygienists (IFDH) reported on a survey of almost 500 hygienist respondents in 20 countries about toothpaste recommendations.[76] Surprisingly, although 80% said that choosing the correct dentifrice was as important as selecting the right toothbrush and was important for good oral health, 40% of respondents weren't recommending a specific fluoride dentifrice to patients, with 58% stating that all fluoride toothpastes are similar. Most agreed that evidence-based knowledge is vital for making product recommendations, but the majority reported limited use of peer-reviewed journals, suggesting there may be a lack of knowledge in the proven gingival (and other oral) health benefits of stabilized stannous fluoride dentifrices relative to dentifrices containing sodium fluoride.[76]

## Antimicrobial Products are not Interchangeable

As shown in Table 2, there is more than one antimicrobial chemotherapeutic product that targets plaque and gingivitis. The bioavailable $SnF_2$ dentifrice reviewed herein is distinct in its breadth of benefits, including effect on plaque virulence. $SnF_2$ formulations have been shown to act in the gingival sulcus where disease begins by interfering with the inflammatory process itself via binding the toxins that would typically trigger a chain of events leading to the edema and bleeding typifying gingivitis.

The multiple therapeutic benefits uniquely offered concurrently in bioavailable $SnF_2$ dentifrices were outlined earlier. What solidifies them as truly 'all-in-one' are the additional features inherent in these multicare toothpastes: tartar control, and the coveted esthetic benefits of stain prevention/whitening.

These advanced $SnF_2$ dentifrices have evolved significantly beyond the early generation $SnF_2$ toothpastes that were thought to be associated with stain and adverse taste in certain patients. With the discovery that $SnF_2$ can be destabilized by other ingredients, a series of formulation innovations were undertaken to ensure optimal bioavailability and the provision of the full range of therapeutic and cosmetic benefits. Current research-supported bioavailable 0.454% $SnF_2$ formulations have been optimized for maximum esthetics and cosmetic benefits with zinc citrate or sodium hexametaphosphate. Numerous clinical investigations including negative and positive (whitening) controls have concurred that the new generation $SnF_2$ dentifrices not only do not promote stain, but in fact provide clinically proven stain-inhibiting and whitening actions for high patient acceptance.[44,45,77,79]

Patients with special oral hygiene concerns and/or those undergoing restorative or certain cosmetic procedures (e.g., dental implants; work that abuts the gingival margin like veneers), are especially vulnerable to the

adverse effects of plaque build-up, where healthy adjacent tissues are integral to the long-term integrity of these procedures.[81-82] Such patients can significantly benefit from the biofilm-inhibiting, bacteriostatic/bactericidal, anti-inflammatory actions of bioavailable $SnF_2$ in areas where mechanical plaque removal can be particularly challenging and an added defense strategy is desirable.

### New Insights show Stannous Fluoride can Benefit both Diseased and Healthy Patients

Recent research shows that in addition to patients with a large number of bleedings sites, healthy subjects (low number of bleeding sites) can similarly see meaningful improvement via plaque toxicity modulation with regular use of a bioavailable $SnF_2$ dentifrice.[37]

In addition to these patient groups with existing gingivitis, another subset of individuals has gingival tissues which appear relatively healthy with little or no bleeding. Their future susceptibility to disease is unknown. Is there a case to be made for these individuals using an antimicrobial bioavailable $SnF_2$ toothpaste? Klukowska *et al* demonstrated that low bleeding, minimally impacted ('healthy') participants still experienced statistically significant reductions in endotoxin and TLR activity with $SnF_2$ usage;[37] this is known to mitigate the inception of inflammation. Just as adults wear seatbelts when driving to protect against harm in a potential accident, antimicrobial $SnF_2$ usage may provide a form of 'insurance' against the otherwise high statistical likelihood of developing gingivitis. **Few other preventive measures are as cost-effective and easy to implement; and promise more in the way of meaningful plaque and gingivitis control.**

## Conclusion

Bioavailable $SnF_2$ has a well-established history for a wide spectrum of therapeutic oral indications based on a myriad of published research establishing clinical effectiveness, including anti-plaque and anti-gingivitis efficacy. In addition to its known bactericidal/bacteriostatic and acid suppression effects, recent research has discovered a new plaque virulence modulation mechanism in which bioavailable $SnF_2$ binds with gingival sulcus pathogenic endotoxins to reduce the inflammatory cascade at its inception stage, and thus prevent or reduce the clinical manifestations of gingivitis irrespective of plaque quantity. The most recent $SnF_2$ dentifrice advancement includes use of the amino acid glycine as a stabilizer for $SnF_2$, leading to greater $SnF_2$ biofilm penetration, LPS neutralization and gingival cell recovery as well as rapid and sustained reductions in gingival bleeding. Regular toothbrushing with properly formulated bioavailable chemotherapeutic antimicrobial $SnF_2$ dentifrice provides an easy to implement strategy not only for patients with existing gingivitis (treatment) but also for those with increased susceptibility or not yet manifesting symptoms (prevention).

## Course Test Preview

To receive Continuing Education credit for this course, you must complete the online test. Please go to: *www.dentalcare.com/en-us/ce-courses/ce579/test*

**1. Which of the following statements is TRUE?**

A. Patients with good oral hygiene are not at risk for developing gingivitis.
B. Host susceptibility is a determinant in gingivitis development.
C. Gingivitis risk can be directly correlated with plaque quantity.
D. Periodontitis is the inevitable outcome of chronic gingivitis.

**2. Clinical research has consistently demonstrated that plaque mass reduction results in a one-to-one proportionate decrease in gingivitis.**

A. True
B. False

**3. Clinical research on the gingival health and plaque reduction benefits of a stabilized stannous fluoride dentifrice has shown _____.**

A. Plaque quantity reduction typically was significantly greater on average than gingivitis/bleeding site reduction.
B. Gingivitis/bleeding site reduction generally was significantly greater on average than plaque quantity reduction.
C. There were generally no significant differences between average plaque quantity reduction and gingivitis/bleeding sites reduction magnitude.

**4. Irritants (e.g., bacteria) and injuries trigger inflammation, a biological defense mechanism. Inflammatory mediators are then sent out which cause characteristic signs of acute inflammation. Cytokine production brings about vascular and cellular permeability effects.**

A. All three statements are true.
B. Only the first statement is true.
C. Only the first and second statements are true.
D. Only the third statement is true.

**5. Acute inflammation can have a positive effect to heal and restore health, while chronic inflammation has been implicated in several systemic conditions.**

A. True
B. False

**6. Subgingival plaque _____.**

A. is generally more virulent than supragingival plaque
B. is predominately composed of anaerobic, gram negative bacteria
C. is predominately colonized by Streptococcus, Haemophilus and Neisseria species
D. A and B

**7. If the gingival 'early lesion' is not restored to homeostasis through removal or modulation of the plaque bacteria, which of the following is likely to occur?**

A. Sloughing
B. Local vasodilation
C. Bone loss

**8. Lipopolysaccharide (LPS) and lipoteichoic acid (LTA) are examples of endotoxins released by _____.**

A. host 'look out' cells (TLRs)
B. cytokines
C. plaque bacteria
D. A and B

**9. Host toll-like receptors (TLRs) in the gingival sulcus identify bacterial endotoxins as harmful, and then _____.**

A. independently fight and remove them
B. activate the inflammatory cascade response
C. become inactivated in their presence
D. A and B

**10. All of the following statements about the gingival inflammatory defense mechanism are true, EXCEPT for one. Which one is the exception?**

A. Toll-like receptors (TLRs) bind and destroy cytokines (e.g., interleukin).
B. Toxic metabolites from plaque pathogens exacerbate the TLR response.
C. The classic manifestations of gingivitis are the end result of the host inflammatory cascade without intervention.
D. In susceptible patients untreated chronic inflammation can lead to tissue destruction and even bone loss.

**11. The most common characteristic clinical signs of inflammation in the gingival tissues include erythema, edema, and altered contours of the gingival margin.**

A. True
B. False

**12. The efficacy of adjunctive chemotherapeutic oral products like stabilized stannous fluoride is contingent upon plaque quantity being concurrently reduced through mechanical means.**

A. True
B. False

**13. With respect to stannous fluoride, which of the following statement(s) is/are correct?**

A. It is only an anticaries agent.
B. It is not substantive.
C. It has a broad range of benefits, including antimicrobial, anti-erosion and anti-dentinal hypersensitivity.

**14. Bactericidal actions, _____, and recently discovered plaque toxicity reduction are all means by which stannous fluoride both prevents and reduces gingivitis.**

A. plaque acid suppression
B. LTA/LPS generation
C. cytokine stimulation

**15. Stannous fluoride acts to prevent inflammation by binding plaque bacteria endotoxins to block the host inflammatory response.**

A. True
B. False

**16. All of the following statements about the way stannous fluoride (SnF2) disrupts the gingival inflammation process by reducing plaque toxicity are true, EXCEPT one. Which is the exception?**

A. Before the host TLRs can mount an inflammatory response to plaque endotoxins, $SnF_2$ binds the endotoxins.
B. $SnF_2$ blocks LTA/LPS from affixing to TLRs.
C. $SnF_2$ initiates the cytokine-driven series of events that leads to inflammation and bleeding.
D. Regular exposure to stabilized $SnF_2$ blunts the adverse effects of plaque endotoxins.

**17. If stannous fluoride's insertion in the inflammatory cascade process leading to gingivitis is compared to an alarm clock set to go off, the alarm clock cord is analogous to _____, and a safety protective cover blocking the outlets is analogous to _____.**

A. plaque endotoxins; toll-like receptors (TLR)
B. stannous fluoride; plaque endotoxins
C. toll-like receptors (TLR); plaque endotoxins
D. toll-like receptors (TLR); stannous fluoride

**18. Klukowska *et al* reported that in a 4-week clinical trial of stannous fluoride with 'high' and 'low' bleeding site cohorts _____.**

A. there was significant improvement (reduction of bleeding sites) in the high but not the low bleeders cohort
B. there was significant improvement (reduction of bleeding sites) in the low but not the high bleeding cohort
C. in both diseased sites as well as in sites not yet showing measurable signs of disease, there were significant benefits

**19. Stannous fluoride's ($SnF_2$) modulation of the virulence/pathogenicity of gingival sulcus plaque has been shown in new research to likely be tied to these key factors _____.**

A. $SnF_2$ supragingival coverage and gingival crevicular fluid absorption
B. Subgingival vascular permeability and osmotic flow
C. $SnF_2$ subgingival penetration and gingival crevicular retention

**20. Formulation expertise is critical for a stabilized stannous fluoride dentifrice because _____.**

A. it will not be maximally efficacious unless formulated with a copolymer
B. it is essential for optimum bioavailability and esthetics
C. A and B

**21. Which of the following statements is TRUE?**

A. Gingivitis is a relatively uncommon condition, except in the elderly.
B. Research shows nearly all patients practice consistent and thorough daily oral hygiene.
C. An oral hygiene practice that is nearly universal is toothbrushing.
D. Patient compliance is likely to be higher when an oral regimen includes more than one product.

**22. Oral chemotherapeutics in common use today include which of the following?**

A. Cetylpyridinium chloride, chlorhexidine, stannous fluoride
B. Arginine, chlorhexidine, stannous fluoride
C. Chlorhexidine, cetylpyridinium chloride, potassium nitrate, stannous fluoride
D. Prescription chlorhexidine gluconate is the only true oral chemotherapeutic

**23. Chlorhexidine works primarily via bactericidal actions. It is considered a gold standard for treating gingivitis. Staining and adverse taste can hinder patient compliance.**

A. Only the first and second statements are true.
B. Only the second and third statements are true.
C. All three statements are true.
D. None of the statements are true.

**24. In recent years, a stannous fluoride dentifrice was introduced with the amino acid glycine as a stabilizer, leading to greater stannous fluoride biofilm penetration.**

A. True
B. False

**25. A consideration in recommending a cetylpyridinium chloride (CPC) antimicrobial is that it _____.**

A. involves potentially adding an additional step (mouthrinse) to the home care regimen
B. has not been evaluated for anti-plaque effectiveness in clinical trials
C. is only available in a dentifrice
D. requires a prescription

**26. Oral chemotherapeutic antimicrobial dentifrices can be an intelligent strategy for improving gingival health because they _____.**

A. are consistent with the common oral hygiene routine of brushing with toothpaste
B. do not require the patient to significantly alter their brushing habits
C. require a prescription and thus bring the patient in for consultation and evaluation
D. A and B
E. B and C

**27. Stannous fluoride is unique among oral antimicrobials in that it _____.**

A. is concurrently an anti-caries agent
B. can be incorporated – if stabilized – into a dentifrice with multiple therapeutic and cosmetic benefits, including plaque virulence modulation to block inflammation
C. A and B

**28. A challenge with early stannous fluoride dentifrices which has been overcome with today's advanced stabilized stannous fluoride formulations was _____.**

A. stain promotion in some users
B. insufficient anti-caries efficacy
C. the need for dual chamber packaging

**29. In subjects with plaque but apparently healthy gingival tissues, susceptibility to later disease is unknown. In-office testing can be done to ascertain individual genetic factors and predict future risk.**

A. Only the first statement is true.
B. Only the second statement is true.
C. Both statements are true.
D. Neither statement is true.

**30. Which of the following statements is FALSE about patient group(s) who could benefit from stabilized antimicrobial stannous fluoride dentifrice use?**

A. Patients who are susceptible to gingivitis, but currently have few observable symptoms, could benefit.
B. Patients with overt signs of gingivitis could benefit.
C. Patients with restorative work, e.g., implants could benefit.
D. Patients with dentinal hypersensitivity should not use stannous fluoride.

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## Additional Resources

- No Additional Resources Available

## About the Author


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Sherri has been a dental hygienist for 43 years. She holds advanced degrees in education. She is associate professor emerita, Southern Illinois University, where she taught oral pathology, public health, and multicultural dental hygiene. Research was concentrated in migrant oral health, pathology, and public health issues, resulting in multiple peer-reviewed publications. She is an approved speaker of and holds a pathology fellowship in the American Academy of Dental Hygiene and is a past president of the Illinois Dental Hygienists' Association. Honors include community service, research, and teacher of the year awards while at SIU, IFLOSS Coalition/Illinois Department of Public Health Oral Health Champion Award, and the Sunstar/RDH Award of Distinction.

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