Dental Caries Management: An Updated Model in the Age of P4 Medicine

Author

V. Kim Kutsch, DMD.

kimkutsch@aol.com

Abstract

Dental caries is a biofilm dysfunction or dysbiosis disease of the dental biofilm characterized by prolonged periods of low pH which results in net mineral loss from the teeth. The disease initiates by acid dissolution of the enamel and eventually creates a cavitation in the enamel, followed by microbial invasion of the tooth. As the disease progresses this process may lead to eventual pulpal tissue death and necrosis and ultimately may mean the loss of the tooth or teeth. Dental caries is biofilm mediated but also host modulated. Despite all the advances in restorative dentistry, this disease remains the most common disease in mankind and the disease burden of dental caries has remained constant. New approaches based on scientific evidence challenge existing paradigms about the etiology, diagnosis and treatment strategies. In the previous century, most treatment for dental caries involved a needle and a drill. But the 21st century ushered in a new era, with the concept of P4 Medicine reflected in a new approach to dental caries management. This paper provides the current scientific evidence of the current biofilm model of the disease, best practices for diagnosis based on risk assessment and targeted treatment strategies to the patient's individual risk factors. The biofilm model of dental caries, rather than pathogen specific, is now understood to be a metabolic issue of the biofilm, producing an acidic environment. The major risk categories for dental caries are reduced saliva flow, dietary issues, biofilm dysfunction and genetic considerations. Treatment strategies include restorative and reparative approaches including antimicrobial, remineralization with fluoride and nano-particle hydroxyapatite, xylitol, silver diamine fluoride, and pH. Behavioral strategies include coaching the patient with routine daily hygiene and also dietary counseling. Caries risk management provides a model of care that is predictive, preventive, personalized and participatory and promises to improve patient outcomes from this disease. This paper describes the most recent best practices for this disease from diagnosis to treatment, and offers an evidenced based philosophy based on current scientific literature and clinical practices.

Introduction

Dental caries is the most common disease in mankind. It is ubiquitous to the human condition and is the number ranked disease by the WHO in virtually every country and every demographic in each country.[1] Traditionally any approach to treating the disease involved surgery, with needles, drills, and perhaps extraction instruments and forceps.[2] Despite previous attempts to treat dental caries by the dental profession, the global burden from this disease has remain unchanged and still represents a serious global health challenge.[3] Dental caries in deciduous and permanent teeth representing the vast majority of oral disease conditions. In an ongoing longitudinal cohort study based on individuals born in Dunedin, New Zealand during 1972 and 1973, they have reported that the dental caries rate has remained constant in these individuals from age 5 through age 38, despite regular traditional dental care.[4] Data from the National Health and Nutrition Examination Survey revealed that for 2015–2016, prevalence of total caries (untreated and treated) was 43.1% and untreated caries was 13.0% among youth aged 2–19 years. Prevalence was lowest in youth aged 2–5 years compared with those aged 6–11 and 12–19 for total (17.7%, 45.2%, 53.5%) and untreated caries (8.8%, 15.3%, 13.4%). While the incidence in youth declined from 50% in 2011-12 to 43% in 2015-16, dental caries is still the most common chronic disease among youth aged 2–19 years.[5] In yet another current systematic review and meta-analysis examining the caries incidence of adolescents, the pooled caries incidence rate was 11% per person per year.[6] The data is pretty clear, dental caries is the most common human disease and traditional treatment strategies have made little to no progress and reducing this disease incidence and health burden.

P4 Medicine Model and Quarternary Prevention

The changing philosophy in medical is being driven by the P4 Medical Model, a term coined by biologist Leroy Hood. The principal tenet of P4 Medicine is that medical practice will be transformed by biotechnology and informatics into a more targeted approach that focuses on managing an individual's overall health as opposed to simply managing their disease. Rather than the medicine of the past that worked on population averages, medicine of the future will focus on the individual. This new approach includes a model that is predictive, preventive, personalized and participatory.[7] Applying these points to traditional dentistry, the surgical dental model fails on each point. The best practice of care for dental caries today is a risk management-based philosophy. Caries risk assessment had been demonstrated to be predictive in clinical trials.[8] It also focuses on preventive strategies, identifying risk factors and developing a regimen to prevent future disease.[9] This prevention approach has a long history in dentistry. Today's preventive dentistry includes not only primary, secondary and tertiary prevention, but also introduces the concept of quarternary prevention. Primary prevention is the health promotion strategies designed to help people avoid the onset of disease and reduce the incidence. These strategies include community water fluoridation and homecare instructions. Secondary prevention is the prevention of recurrence or exacerbation of a disease that has been diagnosed. Tertiary prevention focuses on reducing disease progression and suffering. Quarternary prevention is a new important concept that strives to mitigate unnecessary or excessive intervention of the health care system. New technology developments in diagnostic

instruments also carry the risk of increased surgical intervention that may not be appropriate, while guidelines for non-surgical approaches are improving.[7]

Caries risk management is also personalized as it identifies the specific risk factors contributing to an individual's disease. This leads to a new conversation. Damaged teeth still need to be restored, but now professionals can discuss what's causing the patient's disease. The process then becomes participatory as the professional utilizes wellness coaching techniques to help the patient create personalized strategies for behavioral change to decrease specific caries risk factors. The greatest challenge for the dental profession is to relinquish old approaches based on dental caries being tooth, or tooth surface based and to see it as a whole person disease.[10]

Dental Caries Disease Model

Early disease models focused on identifying a single pathogen responsible for the disease. And at one time the dental profession focused on *Mutans streptococci* as the primary pathologic agent.[11] However, research developed over the past 20 years has clearly established dental caries as a biofilm disease with multiple microbes playing a significant role in the initiation and progression of this disease.[12] Moving beyond a model that is about which specific pathogens are present, the focus is now on how the biofilm is behaving. Is it producing acid for prolonged periods?[13] Disease producing biofilms are now label as cariogenic.[14]

Biofilm Research

Understanding of the oral biofilm has grown significantly. Dental caries once thought to be a disease of *Mutans streptococci*, it is now considered a biofilm dysfunction. Studies have continued to identify new species like *Scardovia wiggsiae*[15], *Slakia exigua*[16] and *Proprionibacterium acidifaciens*[17] as potential pathogens, with or without the presence of *Mutans streptococci*. One of the challenges to the *Mutans streptococci* paradigm is finding the complete lack of this pathogen is populations with severe dental caries.[18] More recently *Candida* species have been added to the list of cariogenic pathogens. Once thought to be nothing more than normal or coincidental inhabitants of the oral biofilm, *Candida albicans*[19,20], *dubliniensis* and *parapsilosis* are now recognized as significant pathogens.[21] While the list of pathogens continues to grow, the research also leads to a better understanding of the environment of the biofilm and its metabolism. In the case of dental caries, the concern is whether the biofilm is producing acid and creating long term acidic conditions on the surface of the teeth. There are multiple causes for this, but these acidic episodes select for cariogenic organisms in the biofilm[22] which leads to expression of the disease in the form of white spot lesions in the enamel and eventually cavitations.

Systemic Concerns

Periodontal disease is now well established as having a relationship with systemic vascular inflammatory diseases.[23] Dental caries may also play a role in arterial diseases in the body. Early research examined both coronary arterial and coronary valve atherosclerotic plaques.[24,25] Typically implicated periodontal pathogens *Prevotella intermedia, Porphyromonas gingivalis* and *Treponema denticola* were found in the plaques, but with greater frequency so was *Streptococcus mutans*. Furthermore, *Streptococcus mutans* with the

cnm gene has the capability to directly invade endothelial cells[26] and has been reported to play a significant role in both bacterial endocarditis[27] and micro-bleeds[28] in the brain. Additionally *Streptococcus viridans* has been discovered in 78% of patients with a myocardial thrombus at sixteen times the level found in the bloodstream, and these patients were thirteen times more likely to have a periapical dental abscess,[29] which might further implicate *Porphyromonas endodontalis*.[30] While more research will provide a clearer picture of any role dental caries might play in peripheral vascular disease, a recent large population based cohort study of data on 247,696 Korean adult men and women, individuals with the severest for of dental caries demonstrated a dose:response relationship to coronary heart disease.[31] Much work remains to be done.

Genetic Factors

Current advances in computer technology have improved the accessibility of GWAS, genome wide association studies. At this point there are numerous genes that have been implicated as having an influence on dental caries risk.[32] Many of these genes are logical, like tooth development genes AMLX1, ENAM, AJAP1 and KALK4.[33,34] Taste influencing genes play a risk in dental caries. The supertaster gene TAS2R38 makes individuals sensitive to phenols found in cruciferous vegetables, while the TAS1R2 genes expresses a preference for sweets.[35] The DQ2 phenotype of the white blood cell antigen reduces an individual's risk for caries.[36] Matrix metalloproteinases are enzymes found in the dentin and play a role in degradation of the bonded dental restoration interface.[37] Protective salivary enzymes include BDEF1, LYZL2 and CA6.[38] Vitamin D absorption may also play a role in dental caries.[39] The science is clear in this developing field, while the exact influence genes may play in the disease, clearly there is some genetic influence in dental caries risk.

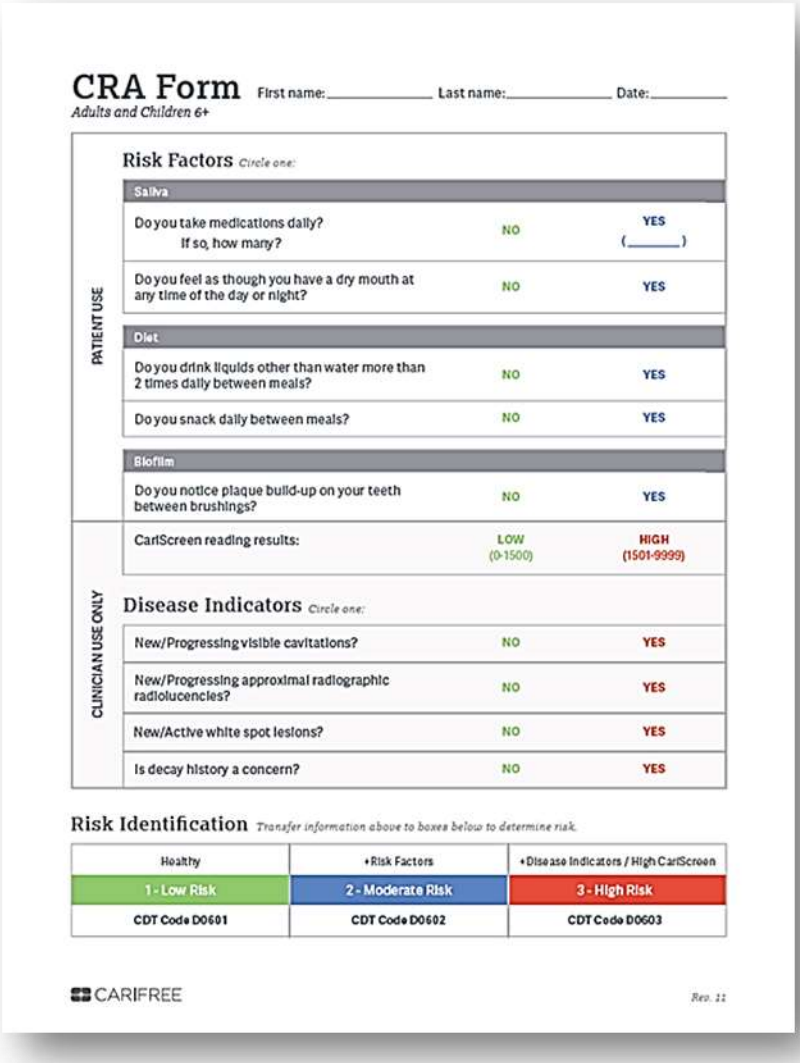
pH

Dental caries is a biofilm mediated and host modulated disease. pH selects for the pathogenic biofilm and behavior, which leads to expression of the disease. Prolonged periods of low pH result in a biofilm shift, leading to demineralization of the enamel and eventual microbial penetration of the tooth. Several sources have proposed utilizing pH as a means to reverse or modulate the disease.[40-42] Marsh first reported the pH selection pressure on the biofilm[22] and has also reported using pH as a treatment strategy.[43, 44] Although pH plays an important role in this disease, oral health products with alkaline pH are limited do to shelf life stability.

Caries Risk Management

Caries risk management represents a new approach to diagnosing and treating dental caries.[45] It involves identifying specific risk factors for individual patients, determining a diagnosis of caries risk and then recommending appropriate therapeutic strategies, that may also include lifestyle and behavioral changes.[46] The first step involves using a risk assessment form for every patient at least one time per year. Several risk assessment forms are available for clinical use and caries risk management is recognized by the American Dental Association.[47] However, upon survey very few clinicians have adapted this philosophy to daily practice.[48] A major impediment to integrating this approach into clinical settings is the process of the risk assessment form itself.[49] In clinical studies, caries risk management has been demonstrated to be predictive, as the baseline caries risk predicts future caries outcomes.[50] It is also preventive.[51] In a clinical trial among high

caries risk adults, the test group had significantly better caries experience than the control group.[52] Caries risk management is personalized, as the process identifies and individualizes risks and specific treatment strategies. It also has a long-term effect on caries outcomes.[53] The test group in another clinical trial demonstrated improved outcomes four years after the study ended. Despite these advantages, caries risk management has not yet been implemented routinely. Filling out a form interview style requires time, and since this task is normally assigned to the hygienist, this creates significant pressure on the hygiene appointment which is already overburdened. Additionally, identifying risks to a patient who doesn't perceive that they have the risk is always a communication challenge as well. The Caries Risk Form in figure 1, solves these major issues by having the patient self- identify and report their risks. This can be accomplished outside of the hygiene operatory and changes the communication dynamic significantly.



CRA Form First name:_____ Last name:_____ Date:_____
Adults and Children 6+

PATIENT USE

Risk Factors *Circle one:*

Saliva		
Do you take medications daily? If so, how many?	NO	YES (_____)
Do you feel as though you have a dry mouth at any time of the day or night?	NO	YES
Diet		
Do you drink liquids other than water more than 2 times daily between meals?	NO	YES
Do you snack daily between meals?	NO	YES
Biofilm		
Do you notice plaque build-up on your teeth between brushings?	NO	YES

CLINICIAN USE ONLY

CariScreen reading results:	LOW (0-1500)	HIGH (1501-9999)

Disease Indicators *Circle one:*

New/Progressing visible cavitations?	NO	YES
New/Progressing approximal radiographic radiolucencies?	NO	YES
New/Active white spot lesions?	NO	YES
Is decay history a concern?	NO	YES

Risk Identification *Transfer information above to boxes below to determine risk.*

Healthy	+Risk Factors	+Disease Indicators / High CariScreen
1 - Low Risk	2 - Moderate Risk	3 - High Risk
CDT Code D0601	CDT Code D0602	CDT Code D0603

CARIFREE Rev. 11

Fig1: Standardized caries risk form with patients self-reporting risk factors.

Risk Factors

The main caries risk factors appear in regular patterns. Being able to recognize these patterns makes the process more efficient.[54] The first major risk is inadequate saliva, creating a dry mouth. This risk is significant because the major protective factor in the mouth is the saliva. In addition to all the protective elements found in saliva, it also is near neutral in pH at rest, and becomes alkaline as soon as food or drink is consumed, already elevating the pH to protect the teeth from damaging demineralization. Saliva output is generally about two liters per day but tends to decrease as part of the aging process. Another complication is prescription medications.[55] The main side effect of many common medications is dry mouth.[56] Other genetic conditions, like Sjogren's Syndrome may further reduce saliva flow.[57] Without the protective elevation of pH, the prolonged acidic episode selects for the wrong microbes, and acidogenic behavior or metabolic output from the oral biofilm. Lack of saliva is further damaging because saliva is supersaturated in nanoparticles of the mineral enamel is made of, carbonated hydroxyapatite crystallites.[58] The body protects the teeth by bathing them in a pH protective solution that is supersaturated with mineral. Patients that present with a salivary risk have a dry appearing mouth, dry tissue and no apparent saliva pooling in the mouth, figure 2. From data collected from private practice over the period of one year by the author, 63% of adults self-identified that they experienced a dry mouth at some time of the day or night. A recent published study indicated 70% of adults experience medication induced xerostomia and rampant caries.[59]

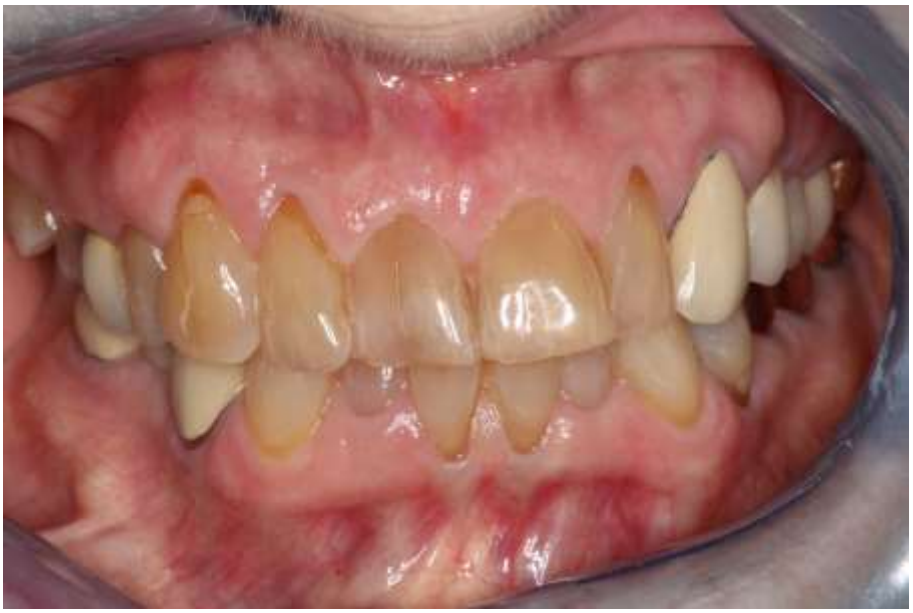


Fig2: Intra-oral appearance of an adult patient with medication induced hyposalivation risk factors.

The next most frequently reported risk factor is diet. In the Western Diet, patients consume an average of 17 teaspoons of sugar per day.[60] Not only is this an issue for obesity, diabetes, hypertension, certain types of cancer and heart disease, it also creates an

acidic environment in the mouth that favors dental caries.[61] Much of the sugar Americans consume is in the form of hidden sugars and sugar sweetened beverages. Not only is the total consumption of sugar a risk for dental caries, but also the frequency.[62,63] Repeated episodes of eating and drinking sugar sweetened foods and beverages results in a prolonged period of low pH in the mouth again selecting for cariogenic microbes and metabolic behavior. Patients that have a dietary caries risk usually present with dental caries lesions spread throughout the mouth geographically, figure 3.

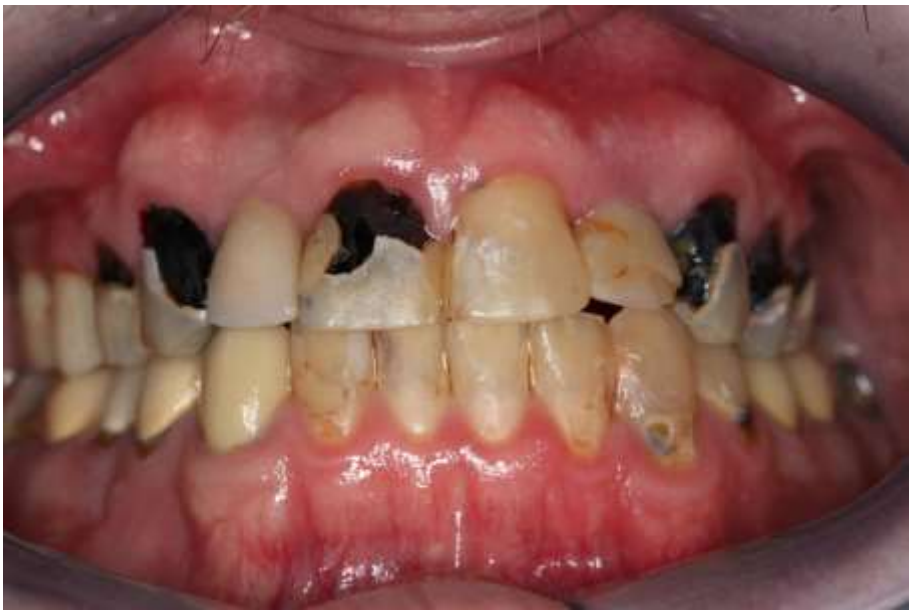


Fig3: Intra-oral appearance of an adult patient with dietary risk factors.

In the same data from the author's private practice, 55% of adults self-identified that they had a dietary caries risk.[59]

The biofilm itself can represent a caries risk. If the patient has too much biofilm load, it increases their risk.[64] Additionally, either having cariogenic microbes predominating the biofilm or having a cariogenic (acidogenic) metabolic output in the biofilm increases risk. The oral biofilm is now being described as healthy, cariogenic or periodontopathogenic.[14] Patients with a biofilm risk typically present with a high biofilm load, evident as excessive plaque buildup on the teeth, figure 4. They may also present with a high ATP score when their dental plaque is tested with bioluminescence.[65-68]

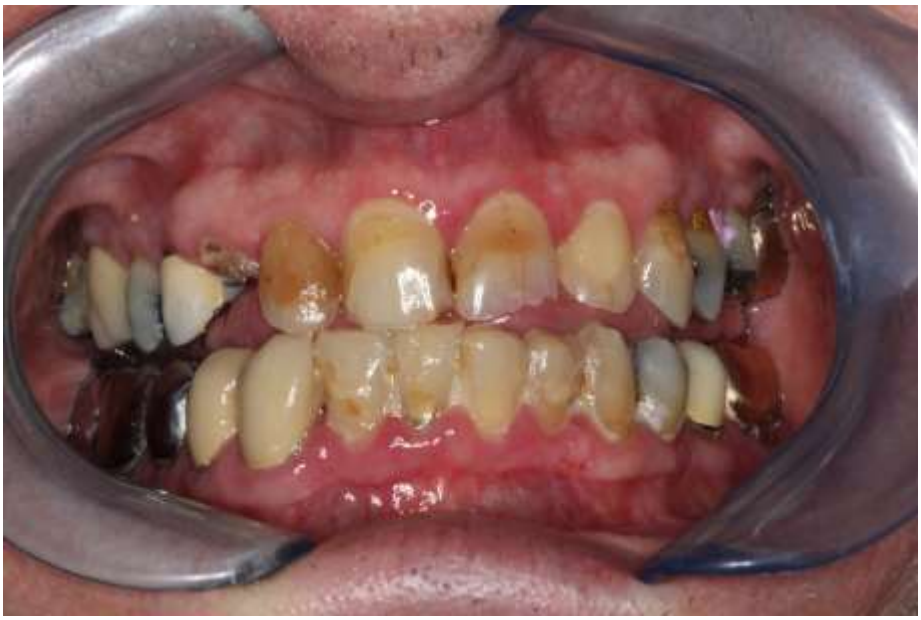


Fig4: Intra-oral appearance of an adult patient with biofilm risk factors.

While dental caries has a genetic component, the exact risk is still undetermined. Consequently, genetic risk factors are left from the caries risk assessment form for now. There are only a few patterns of the teeth that are conclusive for genetic factors.[32] One of these, a polymorphism of the LYZL2 gene, expresses geographically with caries lesions in only the mandibular incisors, figure 5. This is an unusual presentation of dental caries, but few genetic influences provide clear identifiable disease patterns

.

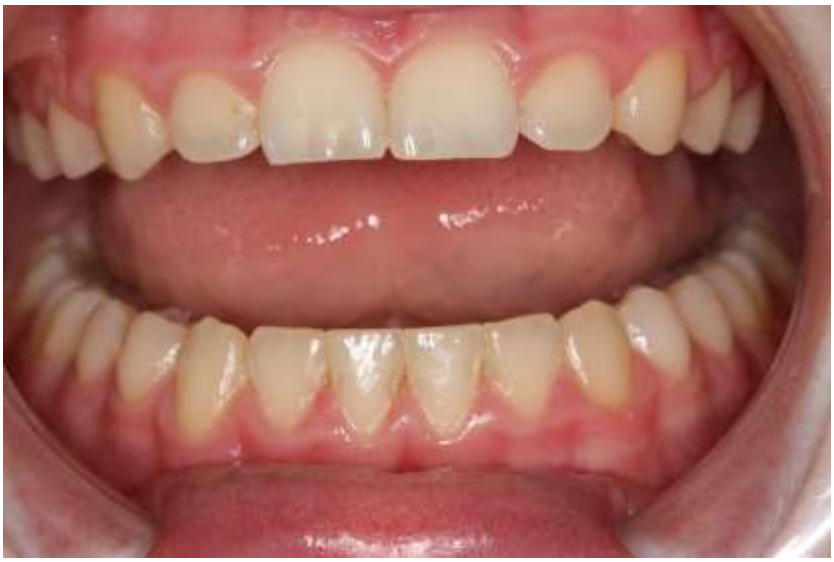


Fig5: Intra-oral appearance of an adolescent patient with LYZL2 genetic risk factor.

Diagnosis of Caries Risk

Making a diagnosis for dental caries risk involves examining all the clinical data available including the practitioner's experience with the patient. This includes the patient's risk factors, disease indicators (presence of caries lesions, active enamel white spot lesions, progressing radiographic radiolucencies, and recent history of caries lesions), the oral exam, and radiographic evidence.[69] Several guidelines for caries risk diagnosis have been proposed, including the ADA guidelines published in 2006 and updated in 2015.[70] Dentistry does not have diagnostic codes, but there are codes for dental caries risk. CDT codes exist for low, moderate and high dental caries risk; D0601, D0602 and D0603 respectively.[71]

Treatment Strategies

Following personalized diagnosis of caries risk, the next step is to consider individualized specific treatment and therapeutic strategies to minimize the patient's risk. At one time the treatment for dental caries consisted exclusively of restoration of the lesion.[72] Today there are numerous opportunities for non-surgical treatment of this disease. ICDAS created a new classification system for lesions, from initiation of the demineralization of the enamel to deep cavitations.[73] Based on the stage of the lesion, non-cavitated lesions can potentially be remineralized and treated non-surgically.[74] The ADA Council on Scientific Affairs has published recommendation for non-surgical intervention which include the use of 38% SDF (silver diamine fluoride), 5% fluoride varnish, 5000 ppm fluoride gel, and 1.23% acidulated phosphate fluoride gel amongst other.[75] A systematic review and meta-analysis of 48 studies concluded the best non-surgical interventions included SDF, pit and fissure sealants, 5% fluoride varnish and 5000 ppm fluoride gel.[76] It is important to note that cavitated lesions still require surgical restoration.

Patients with significant biofilm risk should receive some antimicrobial therapy to reduce their biofilm load. Generally applied as a rinse, the options include the use of commercially available 0.12% chlorhexidine and 0.20% sodium hypochlorite amongst others. Studies provide positive results with both.[77-79.]

pH strategies include the use of neutral and alkaline products to try to raise the oral pH and provide a healthy environment for the biofilm. In silico modelling studies, pH alone predicted to shift the biofilm and reduce the cariogenic organisms.[43] For the patients with hyposalivation, just rinsing with water is an appropriate recommendation to reduce the effects of an acidic episode. Tap water would be the best recommendation as many bottled waters are acidic.[80]

Fluoride has a long history in dentistry as an anticavity strategy. Community water fluoridation was first introduced in 1945 and continues to play a significant in reducing dental caries.[81] Questions have been raised about the appropriateness of community fluoridation in the age pf broad exposure to fluoride in the form of fluoridated dentifrice, fluoride rinses and fluoride treatments following dental exams. Current data still indicates an annual decay incidence reduction of 30% in primary teeth and 12% in permanent teeth from fluoridated water alone.[82] The next most significant therapeutic fluoride utilization is in the form of fluoride varnish.[83] For high caries risk patients this is recommended every three months. Prescription strength fluoride gel with 5000 ppm fluoride provides greater protection that the over the counter 1100 ppm dentifrice. Fluoride is also available in 0.05% fluoride rinses.

Xylitol has long been used as a therapeutic strategy for high caries risk patients. Numerous studies demonstrate the reduction in microbial transmission from mother to child with the regular use of xylitol gum.[84-86] Xylitol also potentiates even small amounts of fluoride.[87] In a clinical trial of 691 high caries risk adults, the test group was given 5 xylitol mints per day. At the end of the 33-month study, the xylitol provided no outcome.[88] However, in secondary analysis of the data, when the participants with root surface lesions (generally associated with dry mouth) were examined separately, the 5 xylitol mints provided a 40% reduction in caries incidence.[89] This study provides support that treatment recommendations should be targeted to patients' specific risk factors.

The body protects the teeth by bathing them in saliva, a supersaturated solution of nano-hydroxyapatite crystallites, the building blocks of enamel.[90] For the patient with hyposalivation, they not only have reduced saliva, but also as a result, reduced mineral exposure to protect the teeth. For these patients it makes sense to provide additional forms of calcium phosphate to their daily hygiene regimen. Nano-hydroxyapatite is biomimetic for the enamel and readily attaches to demineralized enamel surfaces. In multiple studies comparing the remineralizing potential of nano-hydroxyapatite directly to fluoride, nano-hydroxyapatite was comparable to fluoride in some studies and superior to fluoride in others. [91-94]

38% Silver diamine fluoride is a relatively new medicament and appears to reduce caries activity better than fluoride or glass ionomer cements.[95] 38% SDF should be applied at least annually for high risk patients.[96] The result appears to be a combination of the antimicrobial activity of the silver ion, which precipitates in the dentin as microwires, and the remineralization effect forming fluorapatite on the lesion surface.[97,98] The SDF is safe for lesions in children[99] as well as root surface lesions in older adults.[100] The only negative outcome is that SDF turns these lesions jet-black in coloration.101 For some patients this is an acceptable trade-off, while for others it is a serious esthetic concern. Most of the studies conclude that SDF has batter outcomes in lesions limited to enamel rather than deeper lesions involving the dentin.[102]

Probiotics have been studied for caries risk with poor to mixed results. Probiotics are well documented to provide improved outcomes for intestinal issues, but so far, the probiotic use in treatment of dental caries offers little recommendation. Multiple studies demonstrate no outcome when examining probiotics and caries risk.[103-105] One study however did provide an improved outcome. When 261 2-3-year-old preschool children were given probiotic Lactobacillus milk daily for a period of 10 months, their increment for new caries lesions was reduced to 0.58% compared to 1.08% in the control group.[106] More research is needed to determine if probiotics can provide significant benefit in dental caries treatment.

Many of the caries risk factors are behavioral or lifestyle issues and must be addressed individually for each patient. Homecare is an important issue, as the patient must provide adequate daily plaque removal from the teeth. While we take brushing and flossing for granted, they require some level of dexterity to perform effectively. For very young patients, seniors or those with disabilities, this simple task can be quite challenging. While there are only a few studies demonstrating outcomes from daily hygiene self-care, reducing the biofilm load reduces the caries risk.[107] These behaviors need to become habits and

developing new habits can prove difficult and require daily reminders and incentives.[108,109]

Diet is another lifestyle risk factor. Dietary counseling is appropriate for patients with a dietary risk, counseling them on reducing their overall sugar intake or reducing the frequency they consume it. Most patients are also not aware of the amount of hidden sugars present in sugar sweetened beverages, including sodas, athletic and energy drinks, not to mention coffee drinks. While this seems straightforward, a systematic review demonstrated that changing an individual's habits around sugar are more difficult than their behavior with alcohol.[110] None-the-less, there are multiple health benefits from reducing sugar consumption besides dental caries risk. The WHO recommends daily caloric intake goal from sugar be 10% or less and for optimal health should be 3-5%. This amounts to about 2/3 of a teaspoon per day, down from the 25 teaspoons Americans currently consume.[111]

Professional care for dental caries varies by individual risk. A recent systematic review of 10 different caries risk tools pooled the data and indicates that 25% of patients are low caries risk, 14% were moderate caries risk, and 61% high caries risk.[112] Low caries risk patients have no risk factors and no disease indicators. For these patients annual exams, prophylaxis and review of risk factors is adequate. The moderate caries risk patients have at least one risk factor present, but no other signs of the disease. These patients should have re-exams twice a year, prophylaxis and recommendations of proactive strategies to mitigate any risk factors and prevent expression of the disease. High caries risk patients, those patients who have at least one disease indicator, should be seen every three months for exam and prophylaxis and counseling on strategies specifically targeted to their risks for the disease, along with any non-surgical and surgical restorative treatments indicated.

Conclusions

Dental caries is the most common disease in modern man. Traditional approaches to treating this disease usually involved needles, drills and forceps. Today, performing caries risk management provides dental practitioners with an opportunity to provide non-surgical and preventive care that reduces an individual patient's risk for the disease, and provides better outcomes. Caries risk management represents a new standard of practice and meets every criterion of P4 medicine.

References:

1. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJ, et al. Global Burden of Untreated Caries: A Systematic Review and Metaregression. J Dent Res. 2015 May;94(5):650-658.

2. Innes NPT, Chu CH, Fontana M, Lo ECM, Thomson WM, et al. A Century of Change towards Prevention and Minimal Intervention in Cariology. J Dent Res. 2019 Jun;98(6):611-617.

3. Kassebaum NJ, Smith AGC, Bernabé E, Fleming TD, Reynolds AE, et al. Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990-2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors. J Dent Res. 2017 Apr;96(4):380-387.

4. Broadbent JM, Foster Page LA, Thomson WM, Poulton R. Permanent dentition caries through the first half of life. Br Dent J. 2013 Oct;215(7): E12.

5. Fleming E, Afful J. Prevalence of Total and Untreated Dental Caries Among Youth: United States, 2015–2016. NCHS Data Brief No. 307, April 2018.

6. Hummel R, Akveld NAE, Bruers JJM, van der Sanden WJM, Su N. Caries Progression Rates Revisited: A Systematic Review. J Dent Res. 2019 Jul;98(7):746-754.

7. Fiala C, Taher J, Diamandis EP. P4 Medicine or O4 Medicine? Hippocrates Provides the Answer. Applied Laboratory Medicine. September 2019. 4(2):

8. Chaffee BW, Cheng J, Featherstone JD. Baseline caries risk assessment as a predictor of caries incidence. J Dent. 2015 May;43(5):518-24.

9. Chaffee BW, Cheng J, Featherstone JD. Non-operative anti-caries agents and dental caries increment among adults at high caries risk: a retrospective cohort study. BMC Oral Health. 2015 Sep 24;15(1):111.

10. Divaris K. Predicting Dental Caries Outcomes in Children: A "Risky" Concept. J Dent Res. 2015 Dec 8.

11. Banas JA, Drake DR. Are the mutans streptococci still considered relevant to understanding the microbial etiology of dental caries? BMC Oral Health. 2018 Jul 31;18(1):129.

12. Mosaddad SA, Tahmasebi E, Yazdanian A, Rezvani MB, Seifalian A. Oral microbial biofilms: an update. Eur J Clin Microbiol Infect Dis. 2019 Aug 1. doi: 10.1007/s10096-019-03641-9. [Epub ahead of print]

13. Takahashi N. Oral Microbiome Metabolism: From "Who Are They?" to "What Are They Doing?". J Dent Res. 2015 Dec;94(12):1628-37.

14. Colombo APV, Tanner ACR, The Role of Bacterial Biofilms in Dental Caries and Periodontal and Peri-implant Diseases: A Historical Perspective. J Dent Res. 2019 Apr;98(4):373-385.

15. Tanner AC, Mathney JM, Kent RL Jr, et al. Cultivable Anaerobic Microbiota of Severe Early Childhood Caries. J Clin Microbiol. 2011 Feb 2.

16. Tanner ACR, Kent RL, Lif Holgerson P, et al. Microbiota of severe early childhood caries before and after therapy. JDR November 2011. 90(11):1298-1305.

17. Wolff D, Frese C, Maier-Kraus T, Krueger T, Wolff B. Bacterial biofilm composition in caries and caries-free subjects. Caries Res. 2013;47(1):69-77.

18. Johansson I, Witkowska E, Kaveh B, Lif Holgerson P, Tanner AC. The Microbiome in Populations with a Low and High Prevalence of Caries. J Dent Res. 2016 Jan;95(1):80-6.

19. Hemadi AS, Huang R, Zhou Y, Zou J. Salivary proteins and microbiota as biomarkers for early childhood caries risk assessment. Int J Oral Sci. 2017 Nov 10;9(11): e1.

20. Al-Ahmad A, Auschill TM, Dakhel R, Wittmer A, Pelz K, et al. Prevalence of Candida albicans and Candida dubliniensis in caries-free and caries-active children in relation to the oral microbiota-a clinical study. Clin Oral Investig. 2016 Nov;20(8):1963-1971.

21. Lozano Moraga CP, Rodríguez Martínez GA, Lefimil Puente CA, Morales Bozo IC, et al. Prevalence of Candida albicans and carriage of Candida non-albicans in the saliva of preschool children, according to their caries status. Acta Odontol Scand. 2017 Jan;75(1):30-35.

22. Bradshaw DJ, McKee AS, Marsh PD. Effects of carbohydrate pulses and pH on population shifts within oral microbial communities in vitro. J Dent Res. 1989 Sep;68(9):1298-302.

23. Park SY1,2, Kim SH3, Kang SH3,4, Yoon CH3,4, Lee HJ1, Improved oral hygiene care attenuates the cardiovascular risk of oral health disease: a population-based study from Korea. Eur Heart J. 2019 Apr 7;40(14):1138-1145.

24. Fernandes CP, Oliveira FAF, Silva PGDB, Alves APNN, Mota MRL, et al. Molecular analysis of oral bacteria in dental biofilm and atherosclerotic plaques of patients with vascular disease. International Journal of Cardiology. 2014. 174(3):71-712.

25. Oliveira FA, Forte CP, Silva PG, Lopes CB, Montenegro RC et al. Molecular Analysis of Oral Bacteria in Heart Valve of Patients with Cardiovascular Disease by Real-Time Polymerase Chain Reaction. Medicine (Baltimore). 2015 Nov;94(47): e2067.

26. Inenaga C, Hokamura K, Nakano K, Nomura R, Naka S, et al. A Potential New Risk Factor for Stroke: Streptococcus Mutans With Collagen-Binding Protein. World Neurosurg. 2018 May;113: e77-e81.

27. Avilés-Reyes A, Miller JH, Simpson-Haidaris PJ, Hagen FK, Abranches J, Lemos JA. Modification of Streptococcus mutans Cnm by PgfS contributes to adhesion, endothelial cell invasion, and virulence. J Bacteriol. 2014 Aug;196(15):2789-97. doi: 10.1128/JB.01783-14. Epub 2014 May 16.

28. Oliveira FA, Forte CP, Silva PG, Lopes CB, Montenegro RC et al. Molecular Analysis of Oral Bacteria in Heart Valve of Patients with Cardiovascular Disease by Real-Time Polymerase Chain Reaction. Medicine (Baltimore). 2015 Nov;94(47): e2067.

29. Pessi T1, Karhunen V, Karjalainen PP, Ylitalo A, Airaksinen JK, et al. Bacterial signatures in thrombus aspirates of patients with myocardial infarction. Circulation. 2013 Mar 19;127(11):1219-28.

30. Liljestrand JM1, Mäntylä P1, Paju S1, et al. Association of Endodontic Lesions with Coronary Artery Disease. J Dent Res. 2016 Nov;95(12):1358-1365.

31. Kim K, Choi S, Chang J, Kim SM, Kim SJ, et al. Severity of dental caries and risk of coronary heart disease in middle-aged men and women: a population-based cohort study of Korean adults, 2002-2013. Sci Rep. 2019 Jul 19;9(1):10491.

32. Vieira AR, Modesto A, Marazita ML. Caries: review of human genetics research. Caries Res. 2014;48(5):491-506.

33. Shaffer JR, Feingold E, et al. GWAS of Dental Caries Patterns in the Permanent Dentition. Dent Res. 2013 Jan;92(1):38-44.

34. Cavallari T1, Tetu Moyses S, Moyses SJ, Iani Werneck R. KLK4 Gene and Dental Decay: Replication in a South Brazilian Population. Caries Res. 2017;51(3):240-243.

35. Wendell S, Wang X, Brown M, Cooper ME et al. Taste genes associated with dental caries. JDR November 2010. 89(11):1198-1202.

36. Valarini N, Maciel SM, Moura SK, Poli-Frederico RC. Association of Dental Caries with HLA Class II Allele in Brazilian Adolescents. Caries Res. 2012;46(6):530-5.

37. Filho AV, Calixto MS, Deeley K, Santos N, Rosenblatt A, et al. MMP20 rs1784418 Protects Certain Populations against Caries. Caries Res. 2016 Dec 20;51(1):46-51.

38. Ozturk A, Famili P, Vieira AR. The antimicrobial peptide DEFB1 is associated with caries. J Dent Res. 2010 Jun;89(6):631-6.

39. Cogulu D, Onay H, Ozdemir Y, Aslan GI, Ozkinay F, et al. The Role of Vitamin D Receptor Polymorphisms on Dental Caries. J Clin Pediatr Dent. 2016;40(3):211-4.

40. Chapman RJ, Roberts DR, Kugel G. Caries and Periodontal Risk Assessment and Management. Inside Dentistry May 2015. 10(5):56-62.

41. Delgado AJ, Olafsson VG, Donovan T. pH and Erosive Potential of Commonly Used Oral Moisturizers. J Prosthodont. 2015 Jul 27. doi: 10.1111/jopr.12324

42. Delgado AJ, Olafsson VG. Acidic oral moisturizers with pH below 6.7 may be harmful to teeth depending on formulation: a short report. Clin Cosmet Investig Dent. 2017; 9: 81–83. Published online 2017 Aug 3. doi: 10.2147/CCIDE.S140254.

43. Marsh PD, Head DA, Devine DA. Ecological Approaches to Oral Biofilms: Control without Killing. Caries Res. 2015;49 Suppl 1:46-54.

44. Marsh PD. In Sickness and in Health—What Does the Oral Microbiome Mean to Us? An Ecological Perspective. Adv Dent Res. 2018 Feb; 29(1):60-65.

45. Hurlbutt M, Young DA. A best practices approach to caries management.J Evid Based Dent Pract. 2014 Jun;14 Suppl:77-86.

46. Featherstone JDB, Chaffee BW. The Evidence for Caries Management by Risk Assessment (CAMBRA®). Adv Dent Res. 2018 Feb;29(1):9-14.

47. http://www.ada.org/~/media/ADA/Science%20and%20Research/Files/topic_caries_over6.ashx

48. Riley JL 3rd, Gordan VV, Ajmo CT, Bockman H, Jackson MB, et al. Dentists' use of caries risk assessment and individualized caries prevention for their adult patients: Findings from The Dental Practice-Based Research Network. Tex Dent J. 2015 Jan;132(1):18-29.

49. Young DA, Kutsch VK, Whitehouse J. A clinician's guide to CAMBRA: a simple approach. Compend Contin Educ Dent. 2009 Mar;30(2):92-4, 96, 98, passim.

50. Tellez M, Bhoopathi V, Lim S. Baseline Caries Risk Assessment Using CAMBRA May Predict Caries Only in High and Extreme Caries Risk Groups. J Evid Based Dent Pract. 2015 Dec;15(4):197-9.

51. Cheng J, Chaffee BW, Cheng NF, Gansky SA, Featherstone JD. Understanding

treatment effect mechanisms of the CAMBRA randomized trial in reducing caries increment. J Dent Res. 2015 Jan;94(1):44-51.

52. Rechmann P, Chaffee BW, Rechmann BMT, Featherstone JDB. Changes in Caries Risk in a Practice-Based Randomized Controlled Trial. Adv Dent Res. 2018 Feb;29(1):15-23.

53. Evans RW, Clark P, Jia N. The Caries Management System: are preventive effects sustained post clinical trial? Community Dent Oral Epidemiol 2016; 44; 188–197.

54. Kutsch VK. Dental caries: An updated medical model of risk assessment. J Prosthet Dent 2014 April. 11(4):280-5.

55. Kaur M, Himadi E, Chi DL. Prevalence of xerostomia in an adolescent inpatient psychiatric clinic: A preliminary study. Spec Care Dentist. 2015 Dec 21.

56. Kutsch VK, Cady C. Mix Disease: Diagnosis and Treatment. Inside Dentistry Jul/Aug 2009. 5(7):35-38.

57. Donaldson M, Epstein J, Villines D. Managing the care of patients with Sjögren syndrome and dry mouth: Comorbidities, medication use and dental care considerations. J Am Dent Assoc. 2014 Dec;145(12):1240-7.

58. Fejerskov O, Kidd E. Dental Caries: The Disease and its Clinical Management. Blackwell Munksgaard 2003. pp: 56.

59. Quilici D, Zech KN. Prevention and treatment options for medication-induced xerostomia. Gen Dent. 2019 Jul-Aug;67(4):52-57.

60. https://healthyeating.sfgate.com/usda-recommended-sugar-intake-8628.html

61. Lustig R. Fat Chance: Beating the odds against sugar, processed foods, obesity and disease. Penquin Publishers, 2012

62. Bernabé E, Vehkalahti MM, Sheiham A, Lundqvist A, Suominen AL.The Shape of the Dose-Response Relationship between Sugars and Caries in Adults. J Dent Res. 2016 Feb;95(2):167-72.

63. Doichinova L, Bakardjiev P, Peneva M. Assessment of food habits in children aged 6-12 years and the risk of caries. Biotechnol Biotechnol Equip. 2015 Jan 2;29(1):200-204.

64. Doméjean S, White JM, Featherstone JD. Validation of the CDA CAMBRA caries risk assessment--a six-year retrospective study. J Calif Dent Assoc. 2011 Oct;39(10):709-15.

65. Machida CA, MaierT, Iraj Kasimi et al. Bioluminescence and Application in Dentistry, Chapter 1. Bioluminescence. David Rodgerson, Nova Sciences Publisher, 2011.

66. Fazilat S, Sauerwein R, Kimmell I, Finlayson T, Engle J, et al. Application of ATP driven bioluminescence for quantification of plaque bacteria and assessment of oral hygiene in children. Ped Dent May/June 2010. 32(3):195-204.

67. Pellegrini P, Sauerwein R, et al. Plaque retention by self-ligating vs. elastomeric orthodontic brackets: quantitative comparison of oral bacteria and detection with ATP bioluminescence. AJO-DO April 2009. 135(4):426-427.

68. Rechmann P, Chaffee BW, Rechmann BMT, Featherstone JDB. Efficacy of an adenosine triphosphate meter for evaluating caries risk in clinical dental practice. J Am Dent Assoc. 2019 Oct;150(10):873-882.

69. Young DA, Featherstone JD. Caries management by risk assessment.

Community Dent Oral Epidemiol. 2013 Feb;41(1):e53-63.

70. Young DA, Nový BB, Zeller GG, Hale R, Hart TC, et al. American Dental Association Council on Scientific Affairs. The American Dental Association Caries Classification System for Clinical Practice: A report of the American Dental Association Council on Scientific Affairs. JADA June 2015. 146(6):364-365.

71. 2020 CDT Dental Procedure Codes. 2020 ADA publisher.

72. Innes NPT, Chu CH, Fontana M, Lo ECM, Thomson WM, et al. A Century of Change towards Prevention and Minimal Intervention in Cariology. J Dent Res. 2019 Jun;98(6):611-617

73. Dikmen B. Icdas II criteria (international caries detection and assessment system). J Istanb Univ Fac Dent. 2015 Oct 21;49(3):63-72

74. Velo MMAC, Scotti CK, da Silveira ITT, Mondelli RFL, Atta MT, Bombonatti JF. Management of dental caries guided by the ICDAS-LAA: a 28-month follow-up. In Dent. 2019 Sep-Oct;67(5):24-28

75. Slayton RL, Urquhart O, Araujo MWB, Fontana M, Young DA, et al. Evidence-based clinical practice guideline on non-restorative treatments for carious lesions. JADA October 2018. 149(10):837-849.

76. Urquhart O, Tampi MP, Pilcher L, Slayton RL, Araujo MWB, et al. Nonrestorative Treatments for Caries: Systematic Review and Network Meta-analysis. J Dent Res. January 2019. 98(1):12-26.

77. Nascimento MM. The combined use of chlorhexidine and fluoride therapy can reduce the risk for dental caries. Evid Based Dent Pract. 2013 Sep;13(3):123-4. doi: 10.1016/j.jebdp.2013.07.015.

78. Jorgensen MG, Aalam A, Slots J. Periodontal antimicrobials—finding the right solutions. Int Dent J February 2005. 55(1):3-12.

79. Galván M, Gonzalez S, Cohen CL, Alonaizan FA, Chen CT, Rich SK, Slots J. Periodontal effects of 0.25% sodium hypochlorite twice-weekly oral rinse. A pilot study. J Periodontal Res. 2014 Dec;49(6):696-702.

80. Fisher BJ, Spencer A, Haywood V, Konchady G. Relieving Dry Mouth: Varying Levels of pH Found in Bottled Water. Compend Contin Educ Dent. 2017 Jul;38(7):e17-e20.

81. Iheozor-Ejiofor Z, Worthington HV, Walsh T, O'Malley L, Clarkson JE, et al. Water fluoridation for the prevention of dental caries. Cochrane Database Syst Rev. 2015 Jun 18;6:CD010856.

82. Slade GD, Grider WB, Maas WR, Sanders AE. Water Fluoridation and Dental Caries in U.S. Children and Adolescents. J Dent Res. 2018 Sep;97(10):1122-1128.

83. Fernández-Ferrer L, Vicente-Ruíz M, García-Sanz V, Montiel-Company JM, Paredes-Gallardo V, et al. Enamel remineralization therapies for treating postorthodontic white-spot lesions: A systematic review. J Am Dent Assoc. 2018 Sep;149(9):778-786.

84. Lin HK, Fang CE, Huang MS, Cheng HC, Huang TW, et al. Effect of maternal use of chewing gums containing xylitol on transmission of mutans streptococci in children: a meta-analysis of randomized controlled trials.Int J Paediatr Dent. 2016 Jan;26(1):35-44

85. Yates C, Duane B. Maternal xylitol and mutans streptococci transmission. Evid Based Dent. 2015 Jun;16(2):41-2.

86. Muthu MS, Ankita S, Renugalakshmi A, Richard K. Impact of Pharmacological Interventions in Expectant Mothers Resulting in Altered Mutans Streptococci Levels in their Children. Pediatr Dent. 2015 Sep-Oct;37(5):422-8.

87. Maehara H, Iwami Y, Mayanagi H, Takahashi N. Synergistic inhibition by combination of fluoride and xylitol on glycolysis by mutans streptococci and its biochemical mechanism. Caries Research November December 2005. 39(6):521-528.

88. Bader JD, Vollmer WM, Shugars DA, et al. Results from the Xylitol for Adult Caries Trial (X-ACT). J Am Dent Assoc. 2013 Jan;144(1):21-30.

89. Ritter AV, Bader JD, Leo MC, Preisser JS, Shugars DA, Vollmer WM, Amaechi BT, Holland JC. Tooth-surface-specific Effects of Xylitol: Randomized Trial Results. J Dent Res. 2013 Jun;92(6):512-7.

90. Kutsch VK, Kois JC, Chaiyabutr Y, Milicich GW. Reconsidering remineralization strategies to include nanoparticle hydroxyapatite. Compendium March 2013. 34(3):170-177.

91. Pepla E, Besharat LK, Palaia G, Tenore G, Migliau G. Nano-hydroxyapatite and its applications in preventive, restorative and regenerative dentistry: a review of literature. Ann Stomatol (Roma). 2014 Nov 20;5(3):108-14.

92. Zhang M, He LB, Exterkate RA, Cheng L, Li JY, et al. Biofilm Layers Affect the Treatment Outcomes of NaF and Nano-hydroxyapatite. J Dent Res. 2015 Apr;94(4):602-7

93. Vyavhare S, Sharma DS, Kulkarni VK. Effect of three different pastes on remineralization of initial enamel lesion: an in vitro study. J Clin Pediatr Dent. 2015 Winter;39(2):149-60.

94. Daas I, Badr S, Osman E. Comparison between Fluoride and Nano-hydroxyapatite in Remineralizing Initial Enamel Lesion: An in vitro Study. J Contemp Dent Pract. 2018 Mar 1;19(3):306-312.

95. Mei ML, Lo EC, Chu CH. Clinical Use of Silver Diamine Fluoride in Dental Treatment Compend Contin Educ Dent. 2016 Feb;37(2):93-8.

96. Zhi QH, Lo EC, Lin HC. Randomized clinical trial on effectiveness of silver diamine fluoride and glass ionomer in arresting dentine caries in preschool children. J Dent. 2012 Nov;40(11):962-7.

97. Horst JA. Silver fluoride as a treatment for dental caries. Advances in Dental Res. 2018 Feb;29(1):135-140.

98. Mei ML, Nudelman F, Marzec B, Walker JM, et al. Formation of Fluorohydroxyapatite with Silver Diamine Fluoride. J Dent Res. 2017 Sep;96(10):1122-1128.

99. Cheng LL. Limited evidence suggests fluoride mouthrinse may reduce dental caries in children and adolescents. J Am Dent Assoc. 2017 Apr;148(4):263-266.

100. Oliveira BH, Cunha-Cruz J, Rajendra A, Niederman R. Controlling caries in exposed root surfaces with silver diamine fluoride: A systematic review with meta-analysis. J Am Dent Assoc. 2018 Aug;149(8):671-679.

101. Duangthip D, Fung MHT, Wong MCM, Chu CH, Lo ECM. Adverse Effects of Silver Diamine Fluoride Treatment among Preschool Children. J Dent Res. 2018 Apr;97(4):395-401

102. Horst JA, Heima M. Prevention of Dental Caries by Silver Diamine Fluoride. Compend Contin Educ Dent. 2019 Mar;40(3):158-163;

103. Taipale T, Pienihäkkinen K, Alanen P, Jokela J, Söderling E. Administration of Bifidobacterium animalis subsp. lactis BB-12 in early childhood: a post-trial effect on caries occurrence at four years of age. Caries Res. 2013;47(5):364-72.

104. Schwendicke F, Dörfer C, Kneist S, Meyer-Lueckel H, Paris S. Cariogenic effects of probiotic Lactobacillus rhamnosus GG in a dental biofilm model. Caries Res. 2014;48(3):186-92.

105. Villavicencio J, Villegas LM, Arango MC, Arias S, Triana F. Effects of a food enriched with probiotics on Streptococcus mutans and Lactobacillus spp. salivary counts in preschool children: a cluster randomized trial. J Appl Oral Sci. 2018 May 14;26:e20170318.

106. Rodríguez G, Ruiz B, Faleiros S, Vistoso A, Marró ML. Probiotic Compared with Standard Milk for High-caries Children: A Cluster Randomized Trial. J Dent Res. 2016 Apr;95(4):402-7.

107. Macpherson LM, Anopa Y, Conway DI, McMahon AD. National supervised toothbrushing program and dental decay in Scotland. J Dent Res. 2013 Feb;92(2):109-13.

108. Teixeira Alves FB, Kuhn E, Bordin D, Kozlowski VA, Raggio DP, et al. Infant motivation in dental health: Attitude without constant reinforcement. J Indian Soc Pedod Prev Dent. 2014 Jul-Sep;32(3):225-30.

109. Lally p, Van Jaarsveld CM, Potts HWW, Wardle J. How are habits formed: Modelling habit formation in the real world. European Journal of Social Psychology Eur. J. Soc. Psychol. 40, 998–1009 (2010).

110. Evans D. Some evidence that one-to-one dietary interventions in the dental setting can change behaviour. Evid Based Dent. 2012 Jun;13(2):42.

111. https://www.thediabetescouncil.com/45-alarming-statistics-on-americans-sugar-consumption-and-the-effects-of-sugar-on-americans-health/

112. Halasa-Rappel YA, Ng MW, Gaumer G, Banks DA.How useful are current caries risk assessment tools in informing the oral health care decision-making process? J Am Dent Assoc. 2019 Feb;150(2):91-102.e2.