

## Evidence concerning the medical management of caries

Carmen Llana Puy <sup>1</sup>, Leopoldo Forner Navarro <sup>2</sup>

(1) Primary Health Care Dentist, Department 9, Valencian Health Agency

(2) Professor in Dental Pathology and Therapeutics, University of Valencia –Spain

### Correspondence:

Dr. Carmen Llana Puy

C/ Albuixech N<sup>o</sup> 8, pta 2.

46021 Valencia, Spain

E-mail: [llena@uv.es](mailto:llena@uv.es)

Received: 20/06/2007

Accepted: 02/04/2008

Llana-Puy C, Forner-Navarro L. Evidence concerning the medical management of caries. *Med Oral Patol Oral Cir Bucal*. 2008 May;13(5):E325-30.

© Medicina Oral S. L. C.I.F. B 96689336 - ISSN 1698-6946

<http://www.medicinaoral.com/medoralfree01/v13i5/medoralv13i5p325.pdf>

### Indexed in:

-Index Medicus / MEDLINE / PubMed  
-EMBASE, Excerpta Medica  
-SCOPUS  
-Indice Médico Español  
-IBECS

### Abstract

Caries is an infectious, chronic and cumulative disease. It seriously affects quality of life and creates considerable expense for individuals and communities.

The disease can be managed by acting on biofilm formation and maturation, by modifying the kinetics of apatite solution or with a combination of the two processes. This can be achieved by mechanical and chemical control of plaque, appropriate use of fluorides, controlling diet and salivary flow, when possible. Many of these factors depend on the patient's co-operation.

Decisions concerning treatment are influenced by two questions: the scientific evidence for the different alternatives available and each patient's individual caries risk.

The use of different fluoride regimes, depending on the individual risk, remains the most scientifically proven method for avoiding the appearance of new lesions and curbing the speed at which existing ones progress. Chemical control of plaque using chlorhexidine is indicated for patients at high microbiological risk; it is more effective at controlling caries when used in combination with fluorides. Fissure sealing is an effective means of controlling occlusal caries of the molars when the patient's caries risk and the eruptive age of the tooth are taken into account.

**Key words:** Caries, medical management of caries, fluoride, chlorhexidine, pit and fissure sealants.

### Introduction

Dentistry, as a science, aims to achieve optimum oral health levels among the population. Preventive dentistry, as a working approach in every sphere of the profession, aims to keep the population healthy and provide the tools to enable individuals and communities to carry out the personal care tasks that are essential for maintaining their health.

The distribution of some oral diseases, such as caries and periodontal diseases, is almost universal despite the existence of preventive measures of proven efficacy. Initially, the only treatment with any possibility of success was to remove the tooth. Modern Conservative Dentistry provided the basis for the treatment of caries lesions throughout the 20th century. Tooth removal was replaced by restoration wherever possible. This improved

oral health, but after several decades it became clear that something was failing, since 70% of the restorations were replacing existing ones (1), with secondary caries as the most frequent reason for renewing the fillings. The failure of this restoration model led to a re-examination of this approach in the late 20th century.

Based on current knowledge, caries can be defined as a chronic, progressive, cumulative disease which becomes more difficult to control as time passes and its natural course advances. It has a serious effect on the quality of life of those affected and entails considerable expense for individuals and communities.

The knowledge that caries is infectious dates back to 1890, when Miller proposed his chemoparasitic theory. Over 300 species of microorganisms can be identified in the oral cavity, but only those which are able to colonise

the biofilms covering the tooth surfaces can attack the oral tissues (2).

The metabolism of the bacteria within the biofilms causes variations in the pH that affect the dynamic balance of the sub-surface mineralisation of the enamel. A series of factors lead to these metabolic processes resulting in demineralisation of the tooth. They include the bacterial composition of the biofilm, the composition and flow of the saliva, the presence of fermentable carbohydrates and the fluoride, calcium and phosphate concentrations in the oral fluids. The inter-relation of all these factors, which takes place at the interface between the biofilm and the tooth surface, gives rise to a dynamic process of demineralisation and remineralisation. The caries lesion appears when there is an imbalance in favour of demineralisation. The speed of the lesion's progress reflects the activity of the biofilm; this is manifested clinically by an active or an arrested lesion (3).

Consequently, the mechanical era of conservative dentistry has given way to a biological era. Dentistry cannot be practised without reference to the biological factors affecting the patient and the disease. According to this new approach, which may be termed the preventive/restorative model, operative treatment of the lesions (consequences) should be combined with non-operative treatment of caries as an infectious bacterial disease which, in the end, is and will be what determines the control of the disease, resulting in an absence of new lesions, a slower advance of existing ones and better conservation of the restorations that have treated previous lesions.

It has now been scientifically proved that the predictability of the results of operative treatment is directly related to proper control of caries as a disease (4). This way of thinking was already foreshadowed by Black, who argued that "the complete divorcement of dental practice from studies of pathology of dental caries, that existed in the past, is an anomaly in science that should not continue. It has the apparent tendency to make dentists mechanics only". The new perspective signifies a return to the medical aspects of dental practice, following the reflection induced by the failure to achieve a 100% success rate in recent decades despite all the technical resources that have been placed within the dentist's reach.

### **Involving the patient in disease control**

In view of the available scientific evidence, it may be asserted that any patient who wants to achieve a significant improvement in his or her oral health should take an active part in the treatment. The patient is the passive recipient of the symptomatic treatment given by the professional but is active in the aetiological treatment, the part which is nowadays considered fundamental.

As dental caries is a multi-factor disease, there are factors related to it that both the patient and the dentist must accept, since they are, to a certain extent, invariable. These

include the quality of the dental tissues and salivary secretion and composition (5). However, other aetiological factors are directly related to the voluntary habits and attitudes of the patient, such as oral hygiene, dietary habits, application of the preventive measures prescribed and the degree of compliance with the established check-up intervals (6).

All these factors influence the course of the disease in an individual patient, the longevity of restorations and the predictability of results. Nowadays it seems evident that dentists, on their own, do not cure the disease, only its effects or consequences. The patient who wants to treat it properly and avoid further consequences needs to cooperate. However good the method employed during the surgical treatment of the caries lesions, failure is inevitable unless the infectious disease can be controlled, so collaboration is indispensable.

This probably requires a change in attitude, considering that if the patient must take an active rather than a passive role, he or she must also accept that requesting treatment entails obligations if satisfactory results are to be achieved and, finally, must demand not only technical skill of the dentist but also information, training and the adoption of non-operative means to bring the disease under adequate control (7).

### **Preventing dental caries and controlling the progress of the disease**

As biofilms are constantly being formed on the surface of the tooth, fluctuations in pH caused by the metabolic processes taking place within them cannot be avoided, but their cavity formation consequences can (8).

The disease can be brought under control by acting on biofilm formation and maturation, by modifying the kinetics of apatite solution or by a combination of the two processes. This can be achieved through mechanical and chemical plaque control, the use of fluorides, controlling the diet and controlling salivary flow, when possible. Many of these factors depend on how cooperative the patient is, so potentially any person can learn to control the development of the lesion and the progress of the caries.

It should not be forgotten that each individual responds differently to the many complex interrelations between the known and unknown factors that influence this disease, so determination of individual risk is an important prerequisite before planning treatment (2).

Disease control measures such as teaching the patient the best way to remove plaque, apply topical fluorides or modify dietary habits can avoid or at least postpone the appearance of lesions. This concept requires a change of attitude on the part of both patients and dentists, who must decide which is the most cost-effective way to tackle the disease.

Restorative dentistry must go hand-in-hand with implementing non-operative procedures to control caries. To

ignore non-operative therapeutic procedures for managing caries is biologically illogical and ethically unacceptable. For all these reasons, the management of this disease must be thought of as treatment of a continuous caries process and hence of the lesion at all the different stages in its evolution.

Treating caries as an infectious disease that shares risks with other chronic diseases such as diabetes, hypertension, cardiovascular diseases, etc. is a relatively recent concept (9). It leads to looking at dental practice through a less mechanical and more aetiological and pathogenic view of disease and how it is acquired and develops, and to approaching the medical treatment of the disease within a global framework of general health maintenance in the patient and in the community.

In line with current knowledge of the disease and its evolution, the authors propose to review the available scientific evidence regarding the different procedures that are designed to avoid the appearance of new lesions and limit the progress of existing ones, and to suggest applications that can be recommended on the basis of this evidence.

Following the indications of the United States Agency for Health Care Policy and Research guide (10), the degrees of recommendation of the different medical caries treatment procedures have been established as follows: Grade A: at least one randomised controlled clinical trial as part of the body of literature available (levels of evidence Ia, Ib); Grade B: well-designed but not randomised clinical studies (levels of evidence IIa, IIb, III); Grade C: opinions of experts or working groups (evidence level IV).

### Options for medical treatment of caries

#### - *Topical fluorides for professional use*

Although the evidence for the effectiveness of fluorides in reducing the appearance of caries lesions and in slowing the progress of existing lesions is well documented, the clinical trials on the different forms of delivery and their effectiveness do not always agree, showing considerable differences depending on age and on the initial caries risk. Most of the systematic reviews that have been conducted conclude that there is sufficiently conclusive evidence that fluoride varnishes, at different concentrations and with different application regimes, are effective in reducing the appearance of new caries lesions, achieving prevented fractions ranging from 7% to 70% (11).

One such systematic review evaluated the caries reduction effectiveness in primary and permanent teeth of fluoride varnish compared with a placebo or with no treatment and concluded that the estimated prevented fraction was 33% for primary teeth and 46% for permanent teeth (12).

Bader and colleagues (13) reported that topical application of fluoride varnish is the most effective way to reduce caries if only the prevented fraction factor is taken into account, but not if widespread employment of this measure is considered.

The caries reduction benefits of professional applications of fluoride gels (APF 1.23%) compared to a placebo varied between 19% and 33% (14). Studies conducted by Ripa (15) obtained 21.9% to 26.3% caries reductions with one or two applications of gels a year in communities without optimum fluoride concentrations in the drinking water. From the above, it may be concluded that the recommendations for professional application of fluoride gels and varnishes vary according to the caries risk and whether other fluoride delivery methods are used. The administration regime for high risk children and adolescents is twice-yearly application (grade A recommendation). Although high concentration fluoride has also proved beneficial in primary teeth and in high risk adult patients (grade B recommendation), the information on frequency of application for these patients is not sufficiently reliable (16).

#### - *Chlorhexidine*

Chlorhexidine use in gel or varnish form has proved effective in reducing the appearance of new caries lesions in patients at high microbiological risk, reducing caries both occlusally and in the smooth and root surfaces, irrespective of whether it was applied to adults or to children (17). A meta-analysis assessing different clinical studies of the use of chlorhexidine in children aged between 11 and 14 years with high caries risk shows a prevented fraction of 46% obtained by this means, through gels, toothpastes and mouthwashes (18).

The 1% chlorhexidine varnish with thymol (Cervitec®) is the commercial product that has most often been studied, showing 48.6% effectiveness in reducing caries in pits and fissures in the first permanent molar of 6-7-year-old schoolchildren compared to a control group when applied quarterly for two years (19). Three years after the programme was discontinued the benefits had disappeared completely (20).

A systematic review conducted recently established that chlorhexidine varnish has a moderate effect on caries reduction when applications are repeated at 3 to 4 monthly intervals, but when the treatment is discontinued, its effectiveness diminishes after 2 years. Chlorhexidine does not have a caries-preventative effect if applied at lengthy intervals (21).

Other, higher-concentration varnishes such as Chlorzine® or EC40® have proved effective in limiting the progress of active caries lesions and reducing the appearance of new lesions in patients at high microbiological risk.

However, not all the results are conclusive, as a study by Ogaard and colleagues (22) in children wearing orthodontic devices showed that the use of 1% chlorhexidine varnish with thymol did not significantly reduce the number of new white spots due to demineralisation on the labial surface of the teeth, although it did manage to reduce the *S. mutans* levels on these surfaces.

One of the most recent indications for chlorhexidine is to inhibit mother-child transmission of *S. mutans* (23).

It may be concluded that using the various forms of chlorhexidine reduces the risk of caries (grade A recommendation) but their effectiveness declines when the applications are discontinued.

*- Combinations of high-concentration fluoride and chlorhexidine*

Combining chlorhexidine with high-concentration fluoride, delivered in different ways, has proved to be the most effective way of avoiding the appearance of new caries lesions and limiting the speed at which existing ones advance (24). This is very useful in high risk patients, medically compromised patients, the elderly or certain patients in whom carrying out restorative treatment would be difficult. This combination has also proved useful in patients undergoing orthodontic treatment in order to reduce the increase in new caries lesions during the course of these treatments (25).

On analysing the incidence of new caries lesions in head and neck irradiated patients treated with quarterly applications of chlorhexidine and daily fluoride gel, it was found that the number of new caries lesions in these patients, monitored over three years, was comparable to that of the general population in their area (26).

A recent randomised clinical study established that a combination of 0.12% chlorhexidine and 0.05% sodium fluoride significantly reduced the appearance of new caries and the evolution of existing lesions (27).

On the basis of the existing studies, a combination of fluorides and chlorhexidine can be said to present a high level of evidence and may therefore be assigned grade A recommendation, although further controlled clinical studies are needed to establish the most suitable delivery regime for each patient's caries risk.

*- Self-administered fluorides*

Tooth brushing with fluoridated toothpaste, compared to toothpaste without fluoride, brings a 20% to 35% reduction in the incidence of caries, comparable to the 50% improvement obtained in industrialised countries when caries prevalence was very high and water fluoridation programmes were introduced.

Fluoride concentrations below 500 ppm in the toothpaste produce a very limited effect, while 500 ppm increments bring about an additional 6% improvement in the prevented fraction of caries. A concentration of 1000 ppm is considered sufficient for normal toothpastes; 1500 ppm concentrations are only recommended for high risk patients. Consequently, the effectiveness of toothpaste depends on the dose, as has been shown in a systematic review conducted by Ammari in 2003 (28). The recommended frequency is two applications a day; this has been shown to be significantly superior to a single application in permanent teeth among young people (grade A recommendation), whereas the evidence for the effects

of fluoridated toothpaste in primary teeth is incomplete (grade C recommendation) (29).

As regards fluoridated mouthwashes, the most frequently used forms are 0.05% concentrations for daily use or 0.2% concentrations for weekly use. Studies that refer to the effectiveness of this measure have been carried out in populations with high caries indices where other additional fluoride-use measures were not employed. Currently, in view of the widespread use of fluoridated toothpastes, these mouthwashes should only be used by individuals with high caries risk. Collective forms of application such as weekly fluoride mouthwashes in schools should be restricted to communities with low concentrations of fluoride in the water, high or moderate caries prevalence, irregular hygiene practices and/or if fluoridated toothpaste is not used (30).

A systematic review comparing fluoridated toothpaste on its own or combined with other forms of topical fluoride application, in mouthwashes, gels or varnishes, showed that a combination of all these fluoride delivery methods raised the prevented fraction by 10% compared to the use of toothpastes alone. Separate meta-analysis of fluoridated gel or mouthwash combined with toothpaste versus toothpaste alone supports the combined treatments, although the differences were not statistically significant. The only statistically significant result supported the combined use of fluoridated gel and mouthwash compared to gel on its own. Conclusive data could not be obtained from the comparison between the fluoridated varnish/toothpaste combination and toothpaste on its own. The results of this review support the conclusion that topical fluorides (mouthwashes, gels or varnishes) used in addition to fluoridated toothpaste achieve a modest additional reduction in caries compared to toothpaste used on its own. Current clinical practice recommends including some form of additional topical fluoride application (as well as fluoridated toothpaste) for children at high risk of developing dental caries, as increased effectiveness of topical fluorides is expected in children with higher initial DMFS scores; this practice may be considered in populations with a rise in caries of around two surfaces a year (31).

Self-administered gels are only indicated for patients at high risk of caries, basically those with xerostomia or undergoing treatment with orthodontic appliances.

*- Fluoride tablets*

This refers solely to the post-eruptive effects of fluoride administered in the form of tablets. Longitudinal studies of children from three to six years of age, using 1 mg sodium fluoride tablets sucked or chewed, achieved caries reductions of between 20% and 28% (32). The benefits of these programmes could still be seen four years after they had concluded (33).

Studies comparing the efficacy of fluoride tablets with that of other forms of topical application such as fluoridated mouthwashes or toothpastes did not encounter benefits from this form of administering fluoride (34, 35).

The only group for which fluoride tablets can be considered an effective caries reduction measure, with grade C recommendation, is high risk patients living in communities with low-fluoride drinking water who cannot use other fluoride application methods, and only provided that compliance can be guaranteed.

*- Dental sealants*

Pit and fissure sealants are a useful preventive measure to reduce the appearance of occlusal caries in both adults and children. Their effectiveness basically depends on their remaining in place: the caries reduction in the first year ranges between 36% and 100% depending solely on retention.

The teeth that obtain the greatest benefit from this preventive measure are the first and second permanent molars during the first two years following eruption. The importance of carrying out this fissure sealing as soon as possible during the eruptive period must be emphasised, as once eruption is complete and occlusal contact has been attained, the risk of occlusal caries falls (36).

A systematic review that evaluated the effectiveness of fissure sealing compared to no sealing in preventing occlusal caries in children and adolescents demonstrated the effectiveness of his treatment, with 86% caries reduction 12 months later and 57% between 48 and 54 months after treatment. The authors concluded that this measure is clearly effective (grade A recommendation), although it should be applied on the basis of the individual caries risk rather than indiscriminately, as it ceases to be cost-effective when applied to populations with a low risk of caries (37).

A study recently published by Bravo and others followed-up three groups of children for nine years (one control group, one to which fluoride varnish was applied for four years followed by five without, and a further group to which fissure sealants were applied) and found that the fissure sealant group presented a significant reduction in caries compared to the control group (38).

There is disagreement over the progress of very minor lesions that have been sealed, as some authors sustain that the lesion remains free of bacteria for as long the material is retained, and therefore does not progress (39).

*- Xylitol*

Xylitol is a powerful natural sweetener that does not add calories and cannot be consumed by cariogenic bacteria, as its five-carbon chemical structure cannot be recognized by the *Streptococcus mutans*. It can slow down bacterial plaque formation, increase salivary flow and stimulate remineralisation. It has proved useful in slowing the advance of caries lesions and reducing bacterial transmission from mothers to children during the period known as the infection window, at around 21 months of age (grade B recommendation) (40).

Chewing-gums that contain fluoride or chlorhexidine have shown their effectiveness in remineralising caries lesions and in reducing bacterial plaque, respectively, with the additional benefit of increasing salivary flow, although there are no conclusive data regarding the effective doses for these products (41, 42).

**Treatment choice decisions**

New lesions are fewer and the disease advances more slowly in patients who regularly use fluoride compounds. The period between the lesion being limited to the external third of the enamel and its progressing through to the dentine is the appropriate moment to take steps to control the infection, remineralise the enamel and institute procedures to monitor the lesion and the caries risk. This period of time may last for 6 or 8 years. The purpose of treating caries medically is to stretch this period out for as long as possible (43).

Decision-taking is influenced by two questions: the degree to which the different possible alternatives are recommended, based on the existing scientific evidence, and the individual caries risk of each patient (Table 1) (44).

Monitoring the activity of the disease is the most important aspect of caries management. If the process is active, early action to reduce its activity reduces the probability of cavitation. Check-ups at different intervals of time depending on the risk also ensure that suitable treatment is provided according to the needs of each patient, avoiding both over- and under-treatment.

**Table 1.** Medical treatment options based on caries risk.

| Low risk   | Moderate risk  | High risk  |
|--|--|--|
| <ul style="list-style-type: none"> <li>• Diet</li> <li>• Brushing with fluoridated toothpaste at least twice a day</li> <li>• Yearly checkups</li> </ul> | <ul style="list-style-type: none"> <li>• Diet</li> <li>• Brushing with fluoridated toothpaste at least twice a day</li> <li>• Chlorhexidine applications until levels fall to SM &lt; 2.5 x 10<sup>5</sup></li> <li>• Professional fluoride application and checkups every 6 months</li> </ul> | <ul style="list-style-type: none"> <li>• Diet</li> <li>• Brushing with fluoridated toothpaste at least twice a day</li> <li>• Chlorhexidine applications until levels fall to SM &lt; 2.5 x 10<sup>5</sup></li> <li>• Fissure sealing</li> <li>• Daily fluoridated mouthwashes</li> <li>• Professional fluoride application and checkups every 3 months</li> </ul> |

SM: *Streptococcus mutans*

## References

1. Burke FJ, Liebler M, Eliades G, Randall RC. Ease of use versus clinical effectiveness of restorative materials. *Quintessence Int.* 2001 Mar;32(3):239-42.
2. Kleinberg I. A mixed-bacteria ecological approach to understanding the role of the oral bacteria in dental caries causation: an alternative to *Streptococcus mutans* and the specific-plaque hypothesis. *Crit Rev Oral Biol Med.* 2002;13(2):108-25.
3. Paes Leme AF, Koo H, Bellato CM, Bedi G, Cury JA. The role of sucrose in cariogenic dental biofilm formation--new insight. *J Dent Res.* 2006 Oct;85(10):878-87.
4. Baelum V, Van Palenstein Helderman W, Hugoson A, Yee R, Fejerskov O. A global perspective on changes in the burden of caries and periodontitis: implications for dentistry. *J Oral Rehabil.* 2007 Dec;34(12):872-906.
5. Llana-Puy C. The role of saliva in maintaining oral health and as an aid to diagnosis. *Med Oral Patol Oral Cir Bucal.* 2006 Aug;11(5):E449-55.
6. Richards W, Ameen J. The impact of attendance patterns on oral health in a general dental practice. *Br Dent J.* 2002 Dec 21;193(12):697-702.
7. Douglass CW, Sheets CG. Patients' expectations for oral health care in the 21st century. *J Am Dent Assoc.* 2000 Jun;131 Suppl:3S-7S.
8. Fejerskov O. Concepts of dental caries and their consequences for understanding the disease. *Community Dent Oral Epidemiol.* 1997 Feb;25(1):5-12.
9. Petersen PE, Yamamoto T. Improving the oral health of older people: the approach of the WHO Global Oral Health Programme. *Community Dent Oral Epidemiol.* 2005 Apr;33(2):81-92.
10. Coopey M, Nix MP, Clancy CM. Evidence-based practice: AHRQ's role in generating and disseminating knowledge. *AORN J.* 2007 Nov;86(5):857-60.
11. Bader JD, Shugars DA, Bonito AJ. Systematic reviews of selected dental caries diagnostic and management methods. *J Dent Educ.* 2001 Oct;65(10):960-8.
12. Marinho VC, Higgins JP, Logan S, Sheiham A. Fluoride varnishes for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev.* 2002;(3):CD002279.
13. Bader JD, Shugars DA, Bonito AJ. A systematic review of selected caries prevention and management methods. *Community Dent Oral Epidemiol.* 2001 Dec;29(6):399-411.
14. Marinho VC, Higgins JP, Logan S, Sheiham A. Fluoride gels for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev.* 2002;(2):CD002280.
15. Ripa LW. Review of the anticaries effectiveness of professionally applied and self-applied topical fluoride gels. *J Public Health Dent.* 1989;49(5 Spec No):297-309.
16. Hawkins R, Locker D, Noble J, Kay EJ. Prevention. Part 7: professionally applied topical fluorides for caries prevention. *Br Dent J.* 2003 Sep 27;195(6):313-7.
17. Baca P, Muñoz MJ, Bravo M, Junco P, Baca AP. Effectiveness of chlorhexidine-thymol varnish in preventing caries lesions in primary molars. *J Dent Child (Chic).* 2004 Jan-Apr;71(1):61-5.
18. Van Rijkom HM, Truin GJ, Van 't Hof MA. A meta-analysis of clinical studies on the caries-inhibiting effect of chlorhexidine treatment. *J Dent Res.* 1996 Feb;75(2):790-5.
19. Petersson LG, Magnusson K, Andersson H, Almquist B, Twetman S. Effect of quarterly treatments with a chlorhexidine and a fluoride varnish on approximal caries in caries-susceptible teenagers: a 3-year clinical study. *Caries Res.* 2000 Mar-Apr;34(2):140-3.
20. Baca P, Junco P, Bravo M, Baca AP, Muñoz MJ. Caries incidence in permanent first molars after discontinuation of a school-based chlorhexidine-thymol varnish program. *Community Dent Oral Epidemiol.* 2003 Jun;31(3):179-83.
21. Zhang Q, Van Palenstein Helderman WH, Van't Hof MA, Truin GJ. Chlorhexidine varnish for preventing dental caries in children, adolescents and young adults: a systematic review. *Eur J Oral Sci.* 2006 Dec;114(6):449-55.
22. Øgaard B, Larsson E, Henriksson T, Birkhed D, Bishara SE. Effects of combined application of antimicrobial and fluoride varnishes in orthodontic patients. *Am J Orthod Dentofacial Orthop.* 2001 Jul;120(1):28-35.
23. Thorild I, Lindau B, Twetman S. Salivary mutans streptococci and dental caries in three-year-old children after maternal exposure to chewing gums containing combinations of xylitol, sorbitol, chlorhexidine, and fluoride. *Acta Odontol Scand.* 2004 Oct;62(5):245-50.
24. Petersson LG, Magnusson K, Andersson H, Almquist B, Twetman S. Effect of quarterly treatments with a chlorhexidine and a fluoride varnish on approximal caries in caries-susceptible teenagers: a 3-year clinical study. *Caries Res.* 2000 Mar-Apr;34(2):140-3.
25. Zaura-Arite E, Ten Cate JM. Effects of fluoride- and chlorhexidine-containing varnishes on plaque composition and on demineralization of dentinal grooves in situ. *Eur J Oral Sci.* 2000 Apr;108(2):154-61.
26. Llana MC, Bagan JV. Chlorhexidine varnish application and fluoride self-administration for dental caries control in head and neck irradiated patients. A three-year follow-up. *Oral Biosci Med* 2004 Sep;1(3):187-93.
27. Källestål C, Flinck A, Allebeck P, Holm AK, Wall S. Evaluation of caries preventive measures. *Swed Dent J.* 2000;24(1-2):1-11.
28. Ammari AB, Bloch-Zupan A, Ashley PF. Systematic review of studies comparing the anti-caries efficacy of children's toothpaste containing 600 ppm of fluoride or less with high fluoride toothpastes of 1,000 ppm or above. *Caries Res.* 2003 Mar-Apr;37(2):85-92.
29. Twetman S, Axelsson S, Dahlgren H, Holm AK, Källestål C, Lagerlöf F, et al. Caries-preventive effect of fluoride toothpaste: a systematic review. *Acta Odontol Scand.* 2003 Dec;61(6):347-55.
30. Sköld UM. On caries prevalence and school-based fluoride programmes in Swedish adolescents. *Swed Dent J Suppl.* 2005;(178):11-75.
31. Marinho VC, Higgins JP, Sheiham A, Logan S. Combinations of topical fluoride (toothpastes, mouthrinses, gels, varnishes) versus single topical fluoride for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev.* 2004;(1):CD002781.
32. Driscoll WS, Heifetz SB, Korts DC. Effect of chewable fluoride tablets on dental caries in schoolchildren: results after six years of use. *J Am Dent Assoc.* 1978 Nov;97(5):820-4.
33. Driscoll WS, Heifetz SB, Brunelle JA. Caries-preventive effects of fluoride tablets in schoolchildren four years after discontinuation of treatments. *J Am Dent Assoc.* 1981 Dec;103(6):878-81.
34. Driscoll WS, Nowjack-Raymer R, Selwitz RH, Li SH, Heifetz SB. A comparison of the caries-preventive effects of fluoride mouthrinsing, fluoride tablets, and both procedures combined: final results after eight years. *J Public Health Dent.* 1992 Winter;52(2):111-6.
35. Stephen KW, Kay EJ, Tullis JI. Combined fluoride therapies. A 6-year double-blind school-based preventive dentistry study in Inverness, Scotland. *Community Dent Oral Epidemiol.* 1990 Oct;18(5):244-8.
36. Bravo M, Baca P, Llodra JC, Osorio E. A 24-month study comparing sealant and fluoride varnish in caries reduction on different permanent first molar surfaces. *J Public Health Dent.* 1997 Summer;57(3):184-6.
37. Ahovuo-Saloranta A, Hiiri A, Nordblad A, Worthington H, Mäkelä M. Pit and fissure sealants for preventing dental decay in the permanent teeth of children and adolescents. *Cochrane Database Syst Rev.* 2004;(3):CD001830.
38. Bravo M, Montero J, Bravo JJ, Baca P, Llodra JC. Sealant and fluoride varnish in caries: a randomized trial. *J Dent Res.* 2005 Dec;84(12):1138-43.
39. Handelman SL, Leverett DH, Espeland MA, Curzon JA. Clinical radiographic evaluation of sealed carious and sound tooth surfaces. *J Am Dent Assoc.* 1986 Nov;113(5):751-4.
40. Söderling E, Isokangas P, Pienihäkkinen K, Tenovu J, Alanen P. Influence of maternal xylitol consumption on mother-child transmission of mutans streptococci: 6-year follow-up. *Caries Res.* 2001 May-Jun;35(3):173-7.
41. Sjögren K, Ruben J, Lingström P, Lundberg AB, Birkhed D. Fluoride and urea chewing gums in an intra-oral experimental caries model. *Caries Res.* 2002 Jan-Feb;36(1):64-9.
42. Simons D, Brailsford S, Kidd EA, Beighton D. The effect of chlorhexidine acetate/xylitol chewing gum on the plaque and gingival indices of elderly occupants in residential homes. *J Clin Periodontol.* 2001 Nov;28(11):1010-5.
43. Berkey CS, Douglass CW, Valachovic RW, Chauncey HH. Longitudinal radiographic analysis of carious lesion progression. *Community Dent Oral Epidemiol.* 1988 Apr;16(2):83-90.
44. Anusavice K. Clinical decision-making for coronal caries management in the permanent dentition. *J Dent Educ.* 2001 Oct;65(10):1143-6.