



Contents lists available at ScienceDirect

# Japanese Dental Science Review

journal homepage: [www.elsevier.com/locate/jdsr](http://www.elsevier.com/locate/jdsr)

## Guideline

# Evidence-based consensus for treating incipient enamel caries in adults by non-invasive methods: recommendations by GRADE guideline



Mikako Hayashi\*, Yasuko Momoi, Morioki Fujitani, Masayoshi Fukushima, Satoshi Imazato, Yuichi Kitasako, Shisei Kubo, Shoji Nakashima, Toru Nikaido, Akihiko Shimizu, Kenichi Sugai, Rena Takahashi, Masako Unemori, Chinami Yamaki

Department of Restorative Dentistry and Endodontology, Osaka University Graduate School of Dentistry, 1-8 Yamadaoka, Suita, Osaka 565-0871, Japan

## ARTICLE INFO

### Article history:

Received 21 May 2020

Received in revised form

28 September 2020

Accepted 30 September 2020

### Keywords:

Enamel caries

Non-Invasive treatment

GRADE

Clinical guideline

Topical fluoride

## ABSTRACT

Remineralization treatment, which offers the advantage of being non-invasive, is increasingly being used as a minimal intervention treatment in managing incipient enamel caries. The aim of this review was to develop EBM guideline for optimized strategies for non-invasive treatment of incipient enamel caries.

Japanese Society of Conservative Dentistry (JSCD) guideline committee formulated a Guideline for treating incipient enamel caries using the GRADE system, which is the global, mainstream standard for guideline development. The committee selected the most frequent clinical questions (CQs) in treating incipient enamel caries and identified clinically important outcomes in evaluating the efficacy of treatments. Using extensive electronic and manual searches, relevant randomized controlled trials and controlled clinical trials were identified. Based on evidence profiles produced by the committee, the panel discussed the effects, benefits and disadvantages of the selected treatments, as well as their cost effectiveness and feasibility, in order to achieve a consensus in treating incipient enamel caries non-invasively. A recommendation was made for each clinical question after voting by the panel members. Based on the evidence profile and panel discussions for each CQ, the experts strongly recommended application of topical fluoride to inhibit cavitation of incipient enamel caries, and to diminish white spot lesions.

© 2020 Published by Elsevier Ltd on behalf of The Japanese Association for Dental Science This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Remineralization treatment, which offers the advantage of being non-invasive, is being increasingly used as a principal tool of minimal intervention dentistry (MID) treatment in managing caries [1]. Such treatment has several advantages over conventional invasive treatments.

- It conforms with the recommendations of the World Dental Federation advocating MID) [1];
- It is a procedure that respects Nature, since biologically caries is formed as a result of the interplay between demineralization and remineralization and “caries demonstrates a dynamic pathology of sequential demineralisation and remineralization” [2,3];

- It may allow treatment not only of incipient enamel lesions in which the surface is relatively intact, but also of lesions that have penetrated to the dentin, especially when caries risks can be controlled at a low level [4];
- If the lesions are detected early, non-invasive treatment [3] can be applied long-term in order to suppress caries progression and to promote remineralization;
- It will promote better general oral health;
- It is less burdensome for patients mentally, physically and financially.

Unfortunately, currently there are no evidence-based medicine (EBM) guidelines for the best strategies for effective non-invasive treatment to restrict the initial progress of enamel caries.

The International Caries Detection and Assessment System (ICDAS) [5], devised by a group of European and north American researchers in cariology, is a protocol offering international standards for diagnosing and assessing carious lesions. Promoters of ICDAS wanted to lay down a formal definition of various carious

\* Corresponding author.

E-mail address: [mikarin@dent.osaka-u.ac.jp](mailto:mikarin@dent.osaka-u.ac.jp) (M. Hayashi).

lesions. The initial success of ICDAS heightened interest in defining minimally invasive interventions for caries that have formed cavities; but it promoted suggestions on how to remineralize incipient caries that have yet to form cavities. In addition, having found that remineralizing incipient caries is feasible, the ICDAS emphasized the importance of early detection of incipient caries in clinical practice in order to encourage optimal remineralization.

ICDAS categorizes incipient enamel carious lesions into codes 1 and 2 [5]. The clinically recommended non-invasive protocols for controlling caries for these categories are topical fluoride application, high-fluoride sustained-release glass ionomer cement (GIC) application, and sealing with resin-based materials [6].

Topical fluoride application is recommended to prevent caries [7–9]. However, a systematic review found that there is insufficient evidence that topical fluoride is effective in restricting the progression of incipient enamel caries observed as white or brown spots [10]. In addition, once initial enamel lesions progress and form cavities, they can no longer heal naturally [11]. It is necessary to conduct evidence-based clinical trials to verify the effectiveness of topical fluoride in restricting the progression of incipient caries.

GIC hardens as a result of the acid-based reaction in mixing fluoroaluminosilicate glass powder and aqueous polycarboxylic acid [12]. The most prominent feature of this cement is its sustained release and recharge of fluoride ions [12]. Studies have shown that the anticariogenic effects of the material itself [13]. High-fluoride sustained-release GIC, which gradually releases fluoride ions at concentrations several times higher than conventional GIC, has recently been developed to protect dental tissue [14]. Studies are ongoing to investigate whether this material, applied to the surface of incipient enamel caries, can store and supply fluoride ions and thus offer an effective treatment for incipient enamel caries in permanent teeth.

Since the 1970s, many studies have revealed that resin-based materials, such as resinous sealants, suppress the onset of occlusal caries [15]. Various clinical studies have reported the effectiveness of these materials in suppressing the progress of caries, when applied to lesions without clear substantial enamel defects or to relatively minor lesions that penetrate no deeper than half the thickness of the enamel [16]. Such treatments are possible because of advances in resin-based materials, which enable firm adhesion of such materials to the dental tissue, and thus facilitate long-term sealing of the initial caries [17]. A comprehensive evaluation is necessary to examine whether caries progression can be effectively suppressed when incipient enamel caries is sealed with resin-based materials.

Based on the above information, clinical guidelines could be developed describing the effectiveness of topical fluoride application, high-fluoride sustained-release GIC application, and sealing with resin-based materials in the management of incipient enamel caries in permanent teeth. These guidelines should follow the GRADE system [18], the global, mainstream standard for guideline development, and should clarify the quality of the evidence supporting their use. Additionally, these guidelines should take into account the balance between the advantages and burdens of treatments, as well as how they meet patients' values and preferences to determine which methods should be recommended.

## 2. Developing the clinical guidelines for treating incipient enamel caries

### 2.1. Outline of methods for developing the guidelines

The guidelines were developed based on the GRADE system [18]. A guideline committee was set up by consisting of nine university clinicians and two librarians. A chairperson was chosen

at the biannual meeting of the Japanese Society of Conservative Dentistry (JSCD). University clinicians certified as specialists in restorative dentistry by JSCD were then selected by the chairperson and approved by the JSCD general meeting. The committee discussed and selected the most frequent clinical questions (CQs) encountered in treating incipient enamel caries and identified clinically important outcomes when evaluating the efficacy of treatments. Using extensive electronic and manual searches, relevant randomized controlled trials (RCTs) and controlled clinical trials (CCTs) were identified. Evidence profiles, including quality of evidence and summary of findings for each outcome of the CQs, were produced. Panel composed of university researchers, general practitioners, patients and a hygienist discussed the effects, benefits and disadvantages of the selected treatments, as well as their cost effectiveness and feasibility, in order to achieve a consensus in treating incipient enamel caries with non-invasive methods. A recommendation was made for each clinical question by means of voting by the panel members. The provisional guideline was strengthened after reviews and further discussion with university researchers and general practitioners.

### 2.2. Committee members

All 11 university clinicians were experts in conservative dentistry, as certified by JSCD, and actively engaged in teaching students and in clinical work, and six also had dental materials senior advisor's certificates from the Japanese Society for Dental Materials and Devices. One university researcher in cariology, who had experience in developing oral care products in a commercial company, and two librarians were also involved as active members of the group.

### 2.3. Users of the guidelines

Targeted users of the guidelines were dentists and all professionals who deal with incipient enamel caries.

### 2.4. Definition of early enamel caries

Initially, incipient enamel carious lesions targeted in this guideline were defined as those categorized as ICDAS [6] Codes 1 and 2. A lesion of ICDAS Code 3 was subsequently added, since some clinical researches included that lesion.

### 2.5. Clinical questions addressed in developing the guideline

The committee selected the most frequent CQs encountered in treating incipient enamel caries with non-invasive methods. Committee members reached a consensus that the guideline for treating those caries should cover remineralization, protecting and sealing lesions that had not produced cavities or had limited shallow defects.

### 2.6. Outcomes for the clinical questions

The committee discussed and identified critical and important outcomes for patients when treating incipient enamel lesions.

### 2.7. Systematic review methods for clinical questions

#### 2.7.1. Selection criteria of the literatures

Inclusion and exclusion criteria for the selection of papers for the guideline were established prior to the literature search. The inclusion criteria consisted of written clinical studies: systematic reviews, RCTs and CCTs, in which the treatments of incipient enamel caries were described. In the event, there were few RCTs and

CCTs found, so case series were also considered. Since this guideline is focused on permanent teeth, primary teeth were excluded.

### 2.7.2. Search strategy

The journal search, consisting of both electronic and manual searching, was undertaken to identify all relevant studies written in English and Japanese.

#### 1) Electronic databases

An electronic search was conducted by the librarian member of the committee, and included the following databases: PubMed and MEDLINE from 1949 to 2013 and Igaku Chuo Zasshi (Japanese) from 1983 to 2013. The subject search used a combination of controlled vocabulary and free text based on the search strategy for PubMed and MEDLINE (<http://wwwsoc.nii.ac.jp/jscd/mem>). The literature search in Japanese was also conducted using the similar search strategy.

#### 2) Manual searching

The reference lists of all the relevant studies, existing reviews and personal reprint collections of authors were screened for additional relevant publications.

### 2.7.3. Selection of relevant publications

Each publication was initially assessed for relevance by two members using the information presented in the abstract. When an abstract was not available or failed to provide sufficient information, a reprint of the full paper was obtained. When papers or abstracts reported different stages of clinical trials, only the longer-term study was included in the review. The study design of each of the selected papers was assessed by the two reviewers independently in the review process. Systematic reviews, RCTs and CCTs, in which the clinical effectiveness of treating incipient enamel caries in permanent teeth were evaluated, were selected for each clinical question. If a trial was excluded from evaluation, the reasons for exclusion were described.

### 2.7.4. Evaluation of clinical effectiveness

#### 1) Data extraction and synthesis

The following information was extracted from the papers selected for evaluation of the clinical effectiveness of treating incipient enamel caries in permanent teeth: date of the study, year of publication, setting and funding source of the trials, sample size, age and gender of the patients, types of teeth treated, methods of treatments. Information on adverse events or effects was also recorded. Data were extracted for each outcome by two members independently. Data that could be presented in graphs and figures were extracted whenever possible. Such data were only included, however, if both reviewers independently extracted the same result. Any disagreement was discussed, and a third reviewer was consulted as necessary.

#### 2) Evidence profile

The quality of evidence for each outcome of each CQ was assessed and identified by using the RevMan [19] system. Data from identified papers were synthesized to produce a summary of findings. In the case of binary data, relative risk and absolute risk were calculated, while continuous data were compared by average differences. This information was presented in “Evidence profile” tables.

## 2.8. Panel discussion

### 2.8.1. Selection of panel members

A total of nine members; three university researchers (one each from research fields of public health, orthodontics, prosthodontics), two general practitioners, a dental hygienist, a representative of patient, an EBM specialist, a postgraduate student, were called upon to participate in discussions of the guideline.

### 2.8.2. Grading recommendation

Prior to the panel discussion, guideline committee members explained to panel members the background and evidence profile of each CQ. The panel discussion took place to identify the benefits and disadvantages for patients, patients' preferences, clinical impact and cost effectiveness of a proposed intervention. A recommendation for each CQ was finalized by voting by secret ballot by panel members.

## 2.9. External reviewing

The provisional guideline was reviewed by nine external reviewers, who were three university researchers, five general practitioners and one dentist employed by a company. An EBM specialist was included. They were asked to review the provisional guideline based on the AGREE II [20] instrument and to provide any comments from their clinical experiences. The committee discussed the feedbacks from the reviewers and the guideline was strengthened after input and discussion with the reviewers.

## 2.10. Update plan

The guidelines are to be updated every five years.

## 2.11. Source of funding

The guidelines were supported by the funds of the JSCD.

## 3. Clinical guidelines for treating incipient enamel caries

### 3.1. Clinical questions

The following three CQs for treating incipient enamel caries were identified after discussion by the committee.

CQ1. Is the application of topical fluoride effective to arrest incipient enamel caries in permanent teeth?

CQ2. Is the application of GIC with high-fluoride sustained-release effective to arrest incipient enamel caries in permanent teeth?

CQ3. Is sealing by resin-based materials effective to arrest incipient enamel caries in permanent teeth?

### 3.2. Outcomes

The following critical and important outcomes for the CQs were identified after discussion by the committee: critical outcomes, 1) cavitation, 2) diminishing of white spot lesions, important outcomes; 3) smoothing white spot lesions, 4) diminishing radiolucency, 5) diminishing DIAGNOdent values.

### 3.3. Identified clinical researches

Clinical studies identified by electronic and manual searching for each CQ were presented in Tables 1 to 3: four RCTs [21–24] and one observational study [25] for CQ1 (Table 1); one RCT [26] for

**Table 1**  
Summary of evidence of CQ1: Is the application of topical fluoride effective to arrest incipient enamel caries in permanent teeth?

Author	Year	Journal	Design of study	Intervention/Treatment	Control	Assessment method	Results
Agrawal et al. (India)	2011	J Oral Sci.	RCT	Experimental group: 120 patients (Average age 12.8 years old), 604 teeth of active incipient enamel caries, topical fluoride application (1.23% APF gel (12300ppmF) for 4 min) using tray after oral hygiene instruction at the beginning and 6 months later.	Control group: 119 patient (Average 12.8 yrs), 585 teeth of active incipient enamel caries, oral hygiene instruction at the beginning and 6 months later.	Diagnosis of active incipient caries was performed visually. Examination with dental explorer was performed when its suspicious. After 12 months, change of caries lesion number which was assessed as 'no change', 'inactive' and 'progressed' were counted.	Experimental group (APF application twice a year): after 12 months, no change 16.5%, inactive 80.0%, progress 3.5%. Control group: no change 54.0%, inactive 35.6%, progress 10.4%. DMF was not different between experimental and control groups.
Kleber et al. (USA)	1999	J Clin Dent.	Observation study (Patients could choose Enamelon brushing / brushing + tray application)	Experimental group: 9 patients (41 white spots) used Enamelon (tooth paste contains NaF(1130ppmF), 1% CaSO <sub>4</sub> , 1.1% NH <sub>4</sub> H <sub>2</sub> PO <sub>4</sub> ) for tooth brushing (1 min) twice a day and topical application of Enamelon using tray for 5 min after brushing.	Control group: 5 patients (27 white spots) used Enamelon for tooth brushing (1 min) twice a day.	Observation period: 3 months. Change of the white spot area and the color score of white spots (0: shiny, 1: dull, chalky, 2: pitted, loss of surface) were examined.	Lesion area after 3 months: experimental group 6.43 ± 0.44 mm <sup>2</sup> , control group 7.99 ± 0.55 mm <sup>2</sup> . There was a significant difference between experimental and control groups (p < 0.05). Color score: There was a significant difference between experimental and control groups.
Ferreira et al. (Brazil)	2005	Oral Health Prev Dent.	RCT	Group 1 (Topical F application): 126 teeth, brushing instructions once a week and 1.23% APF gel application for 1 min. Group 2 (Non-topical F application): 132 teeth, brushing instructions once a week and placebo gel application for 1 min.	Group 3 (Control): 146 teeth, no intervention.	Observation period: 3 months. Change of plaque score and activeness of white spots were examined.	Plaque score: Group 1 and 2 significantly decreased compared to baseline, however group 3 didn't decrease significantly. Inactivated lesions: Group 1 58%, group 2 57%, group 3 43%. There was a significant difference between group 1, 2 and 3, however there was no difference between group 1 and 2.
Baeshen et al. (Sweden, Saudi Arabia)	2011	Am Orthod Dento-facial Orthop.	RCT	Experimental group: 19 patients, 79 teeth with white spots. 0.5% NaF (2260ppmF) impregnated chewing stick was used 5 times a day for 6 weeks.	Control group: 18 patients, 71 teeth with white spots. Non-fluoride impregnated chewing stick was used 5 times a day for 6 weeks.	DIAGNOdent value and ICDAS II score were compared with baseline data. DIAGNOdent value was measured 3 times and the highest value was accepted.	DIAGNOdent value: After 6 weeks, experimental group significantly decreased compared to baseline, however control group didn't show significant decrease. ICDAS II score: Experimental group significantly decreased after 6 weeks but control group didn't show significant decrease.
Du et al. (China)	2012	Clin Oral Invest.	RCT	Experimental group: 47 patients, 104 white spots. 5% NaF (22600ppmF) varnish (Duraphat) was applied once a month, for 6 times.	Control group: 49 patients, 105 white spots. Saline was applied once a month for 6 times.	DIAGNOdent value at baseline and after 6 months were compared.	5% NaF varnish applied group significantly decreased DIAGNOdent value compared to control group.

CQ2 (Table 2); and two RCTs [27,28] and two quasi-RCTs [29,30] for CQ3 (Table 3) were included.

### 3.4. Evidence profile

The evidence profile of each CQ is summarized in Table 4.

In CQ1, the results of one RCT [22] and one observational study [25] demonstrated that the application of topical fluoride was significantly effective in inhibiting cavitation and diminishing white

spot lesions, respectively. The results of two RCTs [22,24] showed the surfaces of incipient carious lesions were smoothed by the application of topical fluoride in high-risk groups, whereas no changes were seen in low risk groups. The results of two RCTs [21,23] demonstrated the decrease in DIAGNOdent values after the application of topical fluoride. The overall quality of evidence of CQ1 was considered to be high.

In CQ2, the radiographic examinations of one RCT [26] demonstrated significant improvements of radiolucency in interproximal

**Table 2**  
Summary of evidence of CQ2: Is the application of GIC with high-fluoride sustained-release effective to arrest incipient enamel caries in permanent teeth?

Author	Year	Journal	Design of study	Intervention/Treatment	Control	Assessment method	Results
Trairatvorkul et al. (Thailand)	2011	J Dent Res.	RCT	Experimental group:39 initial active caries (proximal white lesion). At baseline, after teeth separation with erastic O ring, GIC (Fuji VII) coating was performed. Fluoride toothpaste was used for daily brushing and topical fluoride application (1.23% APF gel) was performed every 6 months.	Control group: 38 initial active caries (proximal white lesion). At baseline, No coating was performed. Fluoride toothpaste was used for daily brushing and topical fluoride application (1.23% APF gel) was performed every 6 months.	Bite-wing x-ray photo was taken at baseline, 6 and 12 months later and scored as below. Score 1: caries depth was within half of the enamel. Score 2: caries depth was over half of the enamel.	Experimental group: after 12months, 8 teeth improved the score from 2 to 1. Control group: after 12months, 2 teeth improved the score from 2 to 1. (Odds ratio = 6.3, 95%CI 1.3–30.9)

**Table 3**  
Summary of evidence of CQ3: Is sealing by resin-based materials effective to arrest incipient enamel caries in permanent teeth?

Author	Year	Journal	Design of study	Intervention/Treatment	Control	Assessment method	Results
Heller et al. (USA)	1995	J Public Health Dent.	Retrospective study (quasi-RCT)	Experimental group:297 sound teeth surface and 380 initial caries of occlusal surface of permanent teeth. After etching for 30 s, sealant (Delton) was applied and light-cured.	Control group:64 sound teeth surface and 56 initial caries of occlusal surface of permanent teeth. No intervention.	Visual diagnosis and examination by touch manipulation were performed. Initial caries was diagnosed when the tooth surface has dark staining, chalky appearance, sticking on probing, or no apparent visible enamel defects. When it has apparent visible enamel defect, the tooth surface was diagnosed as caries cavity.	Experimental group: after 5 years, 10.8% of initial caries progressed to caries cavity. Control group: after 5 years, 51.8% of initial caries progressed to caries cavity.
Gibson et al. (Canada)	1980	J Canada Dent Assn.	A mouth is divided into 2 and randomized (quasi-RCT)	Experimental group:58 initial caries of occlusal surface of permanent teeth. After etching for 90 s, sealant (bis-GMA self polymerizing red color resin) was applied and light-cured.	Control group:53 initial caries of occlusal surface of permanent teeth. No intervention.	Visual diagnosis and examination by touch manipulation were performed. Progression to caries cavity was diagnosed with x-ray.	Experimental group: after 30 months, 19.0% of initial caries progressed to caries cavity, 3.4% stopped progression and 77.6% improved. Control group: after 30 months, 77.6% of initial caries progressed to caries cavity, 7.5% stopped progression and 15.1% improved.
Martignon et al. (Denmark, Columbia)	2006	Caries Res.	RCT	Experimental group:69 initial proximal caries (no cavity) of permanent teeth. Sealing was performed with Gluma One Bond Adhesive or Concise sealant and ordered to floss 3 times a day.	Control group:69 initial proximal caries (no cavity) of permanent teeth. No intervention was done and ordered to floss 3 times a day.	X-ray diagnosis was performed and scored as below. Score 1: Enamel caries. Score 2: Dentin caries within half of dentin. Score 3: Dentin caries proceeds more than a half of dentin.	Experimental group: after 18 months, 43.5% of initial caries progressed to caries cavity, 17.4% stopped progression and 39.1% improved. Control group: after 18 months, 84.1% of initial caries progressed to caries cavity, 2.9% stopped progression and 13.0% improved.
Alkilzy et al. (Germany)	2009	J Adhesive Dent.	RCT	Experimental group:35 patients, 35 proximal initial caries without cavity. Sealant was performed with polyurethane-dimethylacrylate foil and Heliobond. Dental floss and fluoride tooth paste were used during the term.	Control group:35 patients, 35 proximal initial caries without cavity. No sealant was performed. Dental floss and fluoride tooth paste were used during the term.	X-ray diagnosis was performed and scored as below. D0: No radiolucency. D1: Demineralization at outer half of enamel. D2: Demineralization at inner half of enamel. D3: Demineralization at outer dentin. D4: Demineralization at inner dentin.	Experimental group: after 2yrs, 5.7% of initial caries progressed to caries cavity, 68.6% stopped progression and 25.7% improved. Control group: after 2 yrs, 5.7% of initial caries progressed to caries cavity, 82.9% stopped progression and 11.4% improved.

**Table 4**  
Evidence profiles of CQ1-3.

**CQ1 Is the application of topical fluoride effective to arrest incipient enamel caries in permanent teeth?**

Outcome① Preventing cavitation (Ratio of white spot lesions which didn't develop cavities after 12 months)								Summary of findings		Relative risk [95% CI]	Quality of evidence	Importance	
Quality assessment	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Others	Nos of events/ Nos of white spot lesions (incidence %)	Nos of white spot lesions				
1 <sup>22</sup>	RCT	No	Impossible to evaluate	No	No	Impossible to evaluate	None	Topical fluoride application 584/604 (96.5%)	No fluoride application 524/585 (89.6%)	1.08 [1.04–1.11]	High	Critical	
Outcome② Diminishing white spot lesions (Differences in the areas of white spot lesions (mm <sup>2</sup> ) after 3 months)								Area of white spot lesions		Average difference (95% CI) –1.56(–1.81~–1.31)mm <sup>2</sup>	Very low	Critical	
1 <sup>25</sup>	Observational study	Yes #1	Impossible to evaluate	No	Yes #2	Impossible to evaluate	None	6.43 ± 0.44 mm <sup>2</sup> (n = 41)	7.99 ± 0.55 mm <sup>2</sup> (n = 27)				
Outcome③ Smoothing white spot lesions (Ratio of white spot lesions which got smoothed after 3–12 months)								556/730 (76.2%)		283/717 (39.5%)	1.52 [0.70–3.30]	Low	Important
2 <sup>22,24</sup>	RCT	No	Yes #3	No	Yes #4	No	None	Average DIOGNOdent values		Average difference (95% CI) –3.95 (–5.81~–2.08)	Moderate	Important	
2 <sup>21,23</sup>	RCT	No	No	No	Yes #5	No	None	7.3 (n = 183)	11.3 (n = 176)				

Table 4 (Continued)

<b>CQ2 Is the application of GIC with high-fluoride sustained-release effective to arrest incipient enamel caries in permanent teeth?</b>												
Outcome④ Diminishing radiolucency (Score the depth of caries with bitewing dental x-rays)												
Quality assessment												
Numbers of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Others	Summary of findings Nos of events/ Nos of lesions (incidence %)		Relative risk [95% CI]	Quality of evidence	Importance
								GIC application	No application			
1 <sup>26</sup>	RCT	No	Impossible to evaluate	No	Yes <sup>#6</sup>	Impossible to evaluate	Serious <sup>#7</sup>	8/39 (20.5%)	2/38 (5.3%)	3.90 [0.88~17.18]	Low	Important
<b>CQ3 Is sealing by resin-based materials effective to arrest incipient enamel caries in permanent teeth?</b>												
Outcome① Preventing cavitation : Inspection + palpation + x-ray inspection												
Quality assessment												
Numbers of studies	Study design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Others	Summary of findings Nos of events/ Nos of lesions (incidence %)		Relative risk [95% CI]	Quality of evidence	Importance
								Resin application	No application			
3 <sup>27-29</sup>	RCT = 2, quasi-RCT = 1	No	Yes <sup>#8</sup>	No	No	Impossible to evaluate	None	425/507 (83.8%)	50/178 (28.1%)	2.73 [1.65~4.53]	Moderate	Critical
Outcome④ Diminishing radiolucency												
2 <sup>29,30</sup>	RCT = 1, quasi-RCT = 1	Yes <sup>#9</sup>	No	No	Yes <sup>#10</sup>	Impossible to evaluate	None	36/104 (34.6%)	13/104 (12.5%)	2.77 [1.56~4.91]	Moderate	Important

#1: Only one observational study was available.

#2: There was no control group without using fluoride with high concentration.

#3: The researches showed different results because of the inconsistency in the oral hygiene of patients included.

#4: There is large 95% confidence interval from 0.70 to 3.30 in average difference.

#5: The concentrations of applied fluorides differ between the researches.

#6: There was limitation in evaluation methods of approximal carious lesions.

#7: There was no data about critical outcome.

#8: Heterogeneity is positive. (I<sup>2</sup> = 74%).

#9: There was limitation in the methods of randomization.

#10: The numbers of patients treated was not large enough.

carious lesions after applying GIC with high-fluoride sustained-release. The overall quality of evidence of CQ 2 was low.

In CQ3, the synthesized results of two RCTs [27,28] and one quasi-RCT [29] demonstrated that sealing by resin-based materials significantly inhibited cavitation or progress of carious lesions. Radiographic examinations in one each RCT [30] and quasi-RCT [29] demonstrated significant remineralization after sealing by resin-based materials. The overall quality of evidence of CQ 3 was moderate.

### 3.5. Voting by the panel

In CQ1, all 10 panel members voted in favor of “strong recommendation”. The panels recognized that the quality of evidence of CQ1 was high and there were multiple benefits of fluoride application including its simple clinical method, less technique sensitive, no pain, and its cost effectiveness.

In CQ2, eight panel members voted for “weak recommendation”; whereas two for “weak negative recommendation”. The two who were against the application of GIC cited a numbers of disadvantages including its ineffectiveness in arresting a carious lesion compared to topical fluoride; rougher surfaces after GIC application; causing pain when separating an interproximal lesion; the need for additional visits; and possible plaque accumulation.

In CQ3, eight panel members voted for “strong recommendation”, and two for “weak recommendation”. The minority said the quality of evidence of CQ3 was moderate and there were several disadvantages such as causing pain during teeth separation in treating an interproximal lesion, the needs for additional visits and costs.

### 3.6. Recommendations

Based on the evidence profile and the results of the voting, the following recommendations were proposed by the panel.

CQ1. Application of topical fluoride is effective in inhibiting cavitation of incipient enamel caries, and diminishing and smoothing a white spot lesion. Fluoride application to incipient enamel caries in permanent teeth is recommended. **(Strong recommendation)**

CQ2. Application of high-fluoride sustained-release GIC is recommended to arrest incipient enamel caries (incidental conditions: recommended material, Fuji VII (GC); indication, applicable occlusal and smooth surfaces). **(Weak recommendation)**

CQ3. Sealing by resin-based materials are effective in inhibiting cavitation of incipient enamel caries. However, when this treatment is applied to an interproximal lesion, pain and cost may become burdens on patients. Thus, sealing incipient enamel caries by resin-based materials is conditionally recommended. **(Weak recommendation)**

## 4. Current status and future prospective of developing clinical guidelines of caries treatments

The aim of the guidelines was to aid decision-making by dentists and all professionals who seek to deal with early enamel caries by non-invasive methods. The guidelines were developed pursuant to the GRADE system [18], the global mainstream standard for guideline development. The guidelines thus offer a foundation of recommendations and guidance for making decisions and treatment of incipient enamel caries; but they cannot be a substitute for the judgment of experienced professionals in the actual clinical situation.

Based on the GRADE system [18], the data from relevant studies were summarized each outcome, which was discussed and identified by the committee prior to the literature search. Only limited number of clinical studies was included in all the CQs, because high-quality research work such as RCTs were targeted, and because of

the data synthesis method on each outcome. The GRADE system typically insists on a strict selection of researches. For example, in CQ1 where “cavitation” was set as an outcome, we sought research that investigated whether there was difference in the frequency of cavitation with or without applying topical fluoride to incipient enamel caries lesions. However, there were very few studies [22,25] on arresting and remineralization of incipient enamel caries by topical fluoride, although there are numbers of clinical studies on prevention of caries using fluoride. Further high-quality clinical studies are needed to prove the clinical effectiveness of non-invasive treatment for managing incipient enamel caries.

The committee spent time discussing how best synthesize data from identified clinical studies, especially when there were differences in evaluating methods among these studies. In the case of sealing with resin composite (CQ3), two studies [28,30] used three categories to check the status of incipient caries; remineralized, unchanged and cavitated lesions; but another [29] used two categories, non-cavitated and cavitated lesions. The committee considered that the remineralized and unchanged lesions both indicated positive measures in arresting caries and could be put together as non-cavitated. So the data were synthesized into the two categories, using the utmost care to avoid misinterpretation. The committee fortunately had an opportunity to consult a Cochrane methodological specialist about the statistical technical issues of synthesizing data.

The committee identified the four outcomes and graded them as “serious” or “important” outcomes. Cavitation and diminishing a white spot were chosen as “serious” outcomes, which were considered critical from a patient’s viewpoint. “Remineralization” is often used in cariology researches to evaluate and explain the effects of fluoride or other materials for carious lesions. However, the committee chose the expressions “inhibit cavitation” and “arrest incipient enamel caries” in the CQs and recommendations, since these words better explain patients’ demands for managing caries.

Members of the panel were selected among dental professionals and academics, as well as a patient, in order to include varied opinions as to how to manage incipient enamel caries. The review team and the panel were completely independent. The panel considered the qualities of evidence for each CQ as well as psychological and socio-economical factors of patients. Incidentally, the recommendations by the panel reflected the overall qualities of evidence for each CQ (Table 4).

The panel strongly recommended the topical fluoride application because of the high-quality evidence and the various advantages, such as its simple modality, lack of pain, smooth surfaces treated and its cost effectiveness. However, it should be noted that the research papers did not fit the Japanese clinical experiences because of strict Japanese limits of fluoride concentrations and modalities of application. The committee nevertheless decided to include these researches, because of the consistent positive effects by topical fluoride on arresting enamel incipient caries, when its concentrations were over 1130ppmF<sup>-</sup>. The committee hopes this content of the guideline will be an effective driving force to change the strict regulation of Japanese fluoride materials and will give an impact on oral health promotion by encouraging non-invasive modalities for caries management.

The panel proposed only weak recommendations for sealing with GIC (CQ2) and resin composite (CQ3), because the treated surfaces by both materials became less smooth. In addition, patients may feel pain during the teeth separation for treating an interproximal lesion. The panel members were able to compare the effects of caries management by different modalities as CQs 1, 2 and 3. The modalities in CQs 2 and 3 may be less beneficial for patients because of the chances of pain and need for several visits.

It should be noted that only high-fluoride sustained-release GIC (Fuji VII, GC) is recommended by the Guideline for arrest-



ing incipient enamel caries. Conventional or resin modified GIC is not recommended, since Fuji VII showed approximately four times higher fluoride release compared to conventional GIC [14].

In the Guideline, sealing by resin composite and resin infiltration were considered as different modalities. Resin infiltration was not considered, although some clinical researches were identified during the literature searching [31]. The committee concluded that resin infiltration should not be included in the Guideline, because the treatment is not widely used in clinics and is not covered by Japanese national health insurance.

The committee is planning to update the Guideline within four-year period including latest new evidence of current three CQs as well as new CQs pertaining to remineralizing effects of varnishes containing high-concentration fluoride and CCP-ACP or other calcium materials with various modalities of toothpaste, tooth-cream or gum. For up-dating the guideline, the committee will invite general practitioners and patients to suggest new clinical questions as a way of promoting patients centered care.

The JSCD guideline committee formulated Guideline for treating incipient enamel caries with following the GRADE system, which is the global, mainstream standard for guideline development. The Guideline strongly recommends topical fluoride application to incipient enamel caries in permanent teeth, since it is effective to inhibit cavitation of incipient enamel caries and to diminish and smoothen a white spot lesion.

#### Funding source

This review was developed with funding by The Japanese Society of Conservative Dentistry

#### Conflict of interest

There are no conflict of interest by the all guideline committee members in the review research topic.

#### Acknowledgements

This work is a project of The Japanese Society of Conservative Dentistry. The guideline committee would like to thank Professor Masahiro Yoshida, Dr Hidemichi Yuasa, Dr Yoshihiro Toyoshima, Dr Seiichi Sugiyama and Professor Erika Ota for their support and always helpful and constructive guidance in commenting on the scientific and methodological issues. The committee would also like to pay special tribute to Professor Yoichi Iijima who offered invaluable scientific advice; sadly he died before this publication. The committee thanks Professor Nairn Wilson for his support and helpful and constructive guidance in finalizing this report.

A complete edition, entitled “Clinical guidelines for treating caries” was published in Japanese in June 2015 [32]. This full version is also available in a PDF file at the home page of JSCD (<http://www.soc.nii.ac.jp/jscd/>).

#### References

- [1] FDI World Dental Federation. FDI policy statement on Minimal Intervention Dentistry (MID) for managing dental caries: adopted by the General Assembly; September 2016, Poznan, Poland. *Int Dent J* 2017;67:6–7.
- [2] Holman L, Thylstrup A, Artun J. Surface changes during the arrest of active enamel carious lesions in vivo. A scanning electron microscope study. *Acta Odontol Scand* 1987;45:383–90.
- [3] Nyvad B, Fejerskov O. Scanning electron microscopy of early microbial colonization of human enamel and root surfaces in vivo. *Scand J Dent Res* 1986;94:281–4.
- [4] Ekstrand KR, Kuzmina IN, Kuzumina E, Christiansen ME. Two and a half-year outcome of caries-preventive programs offered to groups of children in the Solntsevsky district of Moscow. *Caries Res* 2000;34:8–19.
- [5] Pitts N. ICDAS—an international system for caries detection and assessment being developed to facilitate caries epidemiology, research and appropriate clinical management. *Community Dent Health* 2004;21:193–8.
- [6] Pitts N, Ekstrand KR. ICDAS Foundation. International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and Management System (ICCMS) - methods for staging of the caries process and enabling dentists to manage caries. *Community Dent Oral Epidemiol* 2013;41:e41–52.
- [7] Walsh T, Wothington HV, Glenn AM, Applebe P, Marinho VC, Shi X. Fluoride toothpastes of different concentrations for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev* 2010;20:CD007868.
- [8] Marinho VC, Wothington HV, Walsh T, Chong LY. Fluoride gels for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev* 2013;11:CD002279.
- [9] Marinho VC, Wothington HV, Walsh T, Clarkson JE. Fluoride varnish for preventing dental caries in children and adolescents. *Cochrane Database Syst Rev* 2015;15:CD002280.
- [10] Bader JD, Shugars DA, Bonito AJ. A systematic review of selected caries prevention and management methods. *Community Dent Oral Epidemiol* 2001;29:399–411.
- [11] Nyvad B, Machiulskiene V, Baelum V. Reliability of a new caries diagnostic system differentiating between active and inactive caries lesions. *Caries Res* 1999;33:252–60.
- [12] McLean JW, Wilson AD. Glass-ionomer cement. *Br Dent Nurs* 2004;196:514–5.
- [13] Benelli EM, Serra MC, Rodrigues Jr JA, Cury JA. In situ anticariogenic potential of glass ionomer cement. *Caries Res* 1993;27:280–4.
- [14] Gandolfi MG, Chersoni S, Acquaviva GL, Piana G, Prati C, Mongiorgi R. Fluoride release and absorption at different pH from glass-ionomer cements. *Dent Mater* 2006;22:441–9.
- [15] Bagramian RA, Graves RC, Bhat M. A combined approach to preventing dental caries in schoolchildren: caries reductions after one year. *JADA* 1976;93:1014–9.
- [16] Griffin SO, Oong E, Kohn W, Vidakovic B, Gooch BF. The effectiveness of sealants in managing caries lesions. *J Dent Res* 2008;87:169–74.
- [17] Jodkowska E. Efficacy of pit and fissure sealing: long-term clinical observations. *Quint Int* 2008;39:593–602.
- [18] GRADE. <http://www.gradeworkinggroup.org> (accessed 2nd May, 2020).
- [19] RevMan 5 in Cochrane Community. <http://community.cochrane.org/tools/review-production-tools/revman-5> (accessed 2nd May, 2020).
- [20] AGREE II instrument. <http://www.agreetrust.org> (accessed 2nd May, 2020).
- [21] Du M, Cheng N, Tai B, Jiang H, Li J, Bian Z. Randomized controlled trial on fluoride varnish application for treatment of white spot lesion after fixed orthodontic treatment. *Clin Oral Invest* 2012;16:463–8.
- [22] Agrawal N, Pushnanjali K. Feasibility of including APF gel application in a school oral health promotion program as a caries-preventive agent: a community intervention trial. *J Oral Sci* 2011;53:185–91.
- [23] Baeshen HA, Lingstrom P, Birkhed PD. Effect of fluoride chewing stick (Miswaks) on white spot lesions in postorthodontic patients. *Am J Orthod Dentofacial Orthop* 2011;140:291–7.
- [24] Ferreira MAF, Latorre MRDO, Rodrigues CS, Lima KC. Effect of regular fluoride gel application on incipient carious lesions. *Oral Health Prev Dent* 2005;3:141–9.
- [25] Kleber CJ, Milleman JL, Davidson KR, Putt MS, Triol CW, Winston AE. Treatment of orthodontic white spot lesions with a remineralizing dentifrice applied by toothbrushing or mouth trays. *J Clin Dent* 1999;10:44–9.
- [26] Trairatvorakul C, Itsaraviriyakul CS, Wiboonchan W. Effect of glass-ionomer cement on the progression of proximal caries. *J Dent Res* 2011;90:99–103.
- [27] Heller KH, Reed SG, Bruner FW, Eklund SA, Burt BA. Longitudinal evaluation of sealing molar with and without incipient dental caries in a public health program. *J Public Health Dent* 1995;55:148–53.
- [28] Gibson GB, Richardson AS. Sticky fissure management. 30-month report. *J Can Dent Assoc* 1980;46:255–8.
- [29] Martignon S, Ekstrand KR, Ellwood R. Efficacy of sealing proximal early active lesions: an 18-month clinical study evaluated by conventional and subtraction radiography. *Caries Res* 2006;40:382–8.
- [30] Alkilzy M, Berndt C, Meller C, Schidlowski M, Splieth C. Sealing of proximal surfaces with polyurethane tape: a two-year clinical and radiographic feasibility study. *J Adhes Dent* 2009;11:91–4.
- [31] Borges AB, Caneppele TM, Masterson D, Maia LC. Is resin infiltration an effective esthetic treatment for enamel development defects and white spot lesions? A systematic review. *J Dent* 2017;56:11–8.
- [32] The Japanese Society of Conservative Dentistry. Clinical guidelines for treating caries. second ed. Kyoto: Nagasue Syoten; 2015. p. 1–114.