Silver Diamine Fluoride 38%

Scientific Literature Review

May 2023

Silver Diamine Fluoride (SDF) 38% has been receiving a great deal of attention by U.S. dental professionals since it was cleared for use by the Food and Drug Administration in August 2014 under the provisions of the Federal Food, Drug and Cosmetics Act. The Cleared Indication for Use is, “Treatment of dentinal hypersensitivity. For use in adults over the age of 21.” In addition, in October of 2016 the U.S. Food and Drug Administration (FDA) granted “Breakthrough Therapy Designation” to Advantage Arrest® Silver Diamine Fluoride 38% for the arrest of tooth decay in children and adults.

In the age of the internet, access to credible information about the history, safety, and efficacy of SDF is important. In addition, a significant number of national and local television news programs and social media postings have communicated information about the use of SDF for the treatment of carious lesions in all populations.

SDF has been used by dental professionals outside the U.S. for both the treatment of dentinal hypersensitivity and as a caries therapy for more than 50 years. This review is intended to provide U.S oral health professionals with an understanding of the history of SDF around the world, including the most current information regarding use in the U.S.

Under federal law, the use of a drug or medical device by a licensed medical professional for an indication not Approved or Cleared by the FDA is allowable and not uncommon. This is termed “off-label” use.

As the organization permitted to market the first FDA Cleared SDF product in the United States, (Advantage Arrest Silver Diamine Fluoride 38%,) it is our intention to provide a review of all scientific literature available to us to help ensure that oral health professionals, and through them their patients, are well informed about this therapy.

This document is not assumed to contain all published information regarding SDF, as that would be virtually impossible, since SDF has been in use in many countries for decades. It is however meant to provide a fair and balanced view of the benefits and risks of the use of SDF. If, after reading this document you have any questions, please send an email to the address below and we will get back to you promptly.

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Frequently Asked Questions

Since the launch of Advantage Arrest Silver Diamine Fluoride 38% in April, 2015 we have fielded questions from oral health professionals on a range of subjects including Clinical Application, Safety, Precautions, Restorative Aspects, Insurance Coding and Reimbursement.

Clinical Application

1. **Since the FDA cleared Advantage Arrest Silver Diamine Fluoride 38% (SDF) for the treatment of hypersensitivity, with fluoride varnish as the comparative device, is this clinical application the same as fluoride varnish?**

   For the site-specific control of hypersensitivity, the technique to apply Advantage Arrest is similar to that of fluoride varnish. SDF is not for generalized or full mouth applications. Read the package insert for full application and precaution instructions.

2. **I currently use fluoride varnish off-label as an in-office fluoride treatment for caries prevention or to attempt caries arrest. Can I use Advantage Arrest in this same way?**

   Yes. However, Advantage Arrest is only applied site-specifically on carious lesions or high-risk sites such as non-sealed occlusal surfaces or interproximal areas where incipient lesions are suspected. Care should be taken to isolate each cleaned application site with cotton rolls. The metallic taste and propensity to temporarily stain soft tissue/skin and permanently stain demineralization make the application of silver diamine fluoride different than the generalized full-mouth application associated with fluoride varnishes.

   Many clinicians apply SDF site specifically and then apply a fluoride varnish generally. In some cases, this can help keep SDF in contact with the treatment site in patients that cannot sit for the recommended 1-minute soaking period.

   The chemical action of the SDF occurs almost immediately in the outer layers of the softened enamel and/or dentin and can be confirmed by changes in the hardness and density of the treated surface, like caries that arrests naturally because of positive changes in oral hygiene, diet, or daily application of fluoride in custom trays. The darkening of the lesion occurs over 24 hours and may increase over a week. Reexamination of the lesion and reapplication of SDF may be warranted to ensure caries arrest. Reapply SDF at regular recalls until the tooth is restored or exfoliates.

3. **Does Advantage Arrest prevent caries only at the point of application and adjacent sites?**

   No. When applied to a carious lesion or at-risk site, Advantage Arrest has demonstrated the ability in studies summarized in this packet to act as a reservoir for silver and fluoride. The silver is bactericidal against cariogenic biofilm not only at the site but has a halo effect as saliva flows throughout the oral cavity. The same is true for the fluoride, helping to promote remineralization and prevent demineralization on all dentition.

4. **Is there a recommended frequency of application of SDF for caries control?**

Caries arrest studies were conducted with SDF applications of once and twice annually, with twice annual applications demonstrating the best benefit. Arrested lesions were retreated every 6 months.

Clinicians have reported that they will recall their first cohort of SDF patients within 3-6 weeks to evaluate the application and action of the treatment. Once they have a feel for the predictability of the material with their application technique, they will set recall appointments based on the risk level and caries activity of the patient with higher risk patients at 3 month intervals. Moderate to high-risk patients, where it appears that home care and diet counseling has had positive impact, are recalled at 6 months.

5. **Does the application of SDF to a lesion cause discoloration?**

Darkening of decayed and demineralized sites occurs as the lesion arrests. Healthy tooth structure does *not* stain with the application of silver diamine fluoride.

This process is similar to what is seen when caries arrests due to changes in diet or increased use of other fluorides. A recent study showed that patients see the discoloration as a clear indication that the treatment is working. Similar to the treatment of eroded and hypersensitive dentin, the treated area can be restored using glass ionomer or with a sandwich restoration of both glass ionomer and composite.

Silver diamine fluoride 38% should not be diluted in an attempt to reduce discoloration. Studies have shown that diluted solutions may not be effective for caries arrest.

Ionic silver adsorbs onto almost any protein surface and is especially tenaciously bound to denatured proteins. This accounts for the specificity to carious collagen over normal collagen, but both will stain. The differentiator between these stains is that with SDF use intrinsic pigmentation of a carious lesion occurs and surface protein staining occurs primarily on healthy tissue. These oxides are bound to the tissue and don't easily wash or polish away. This is why the blackened lesion retains its dark color and is most likely the reason the antimicrobial effect is long-lasting.

The functional indicator of effectiveness is when the silver oxide is bound to the diseased collagen. If the surface doesn't turn grey/black, the silver didn't bind and the antimicrobial effect will only be short-lived. Darkened arrested lesions will gradually lose their black appearance over several years, and reapplication is indicated.

6. **Are there any studies, reports or articles on parent/patient reaction to lesion staining caused by application of SDF?**

Yes, through June of 2021 there have been several published studies/surveys and posters presented on this topic; all showing similar results. One of these studies is listed below, and others are in the reference section of this review packet citations 90-95.

Parental Perceptions and Acceptance of Silver Diamine Fluoride Staining, YO Crystal, MN Janal, DS Hamilton and R Niederman, J Am Dent Assoc., Jul 2017

The aim of the study was to assess parental perception of SDF staining and to determine whether parents' level of acceptability of SDF would change with the location in the mouth, the child's behavior and demographic factors. A diverse group of 120 parents (98 mothers and 22 fathers) were surveyed. 67.5% of those surveyed judged SDF staining to be esthetically tolerable on posterior teeth, with only 27.9% making this same assessment if the stain was located in the anterior region. In the absence of behavioral barriers to conventional restorative treatments 53.6% of parents were likely to choose SDF on posterior teeth, while only 26.9% would choose SDF for anterior areas. The level of acceptance increased as children's behavioral barriers increased. At the extreme, when provided the option of general anesthesia, acceptance of SDF application increased to 68.5% in the posterior and to 60.3% on anterior teeth. Socioeconomic status did impact acceptance of treatment.

Four major findings were presented:

• Acceptance of SDF staining was greater in posterior than the anterior teeth

• Acceptance levels increased as the child required more advanced methods of behavior guidance

• The effects of location and cooperation changed with socioeconomic status

• Only approximately one-third of parents found SDF to be unacceptable under any circumstances

Discussion emphasized the need for parental/patient informed consent forms for the application of SDF.

Effect and Acceptance of Silver Diamine Fluoride Treatment on Dental Caries in Primary Teeth, J Clemens, J Gold, J Chaffin, J Pub Hlth Dent, July 2017

This study enrolled 32 pre-cooperative children aged 2-5 years with 118 active caries lesions in primary teeth. Teeth were treated with SDF and children were recalled at two weeks (assess color, hardness, pain and a parent survey was conducted on ease, taste, discoloration and painlessness) and at 3 months (assess color, hardness and pain). Survey results showed:

• 90.0% strongly agreed or agreed with the statement "SDF application is an easy process."

• 86.6% strongly agreed or agreed with the statement "I am comfortable with discoloration of cavities after SDF."

• 93.3% strongly agreed or agreed with the statement "SDF application was pain free."

• 86.6% strongly agreed or agreed with the statement "The taste of SDF was acceptable."

7. **Will Advantage Arrest stain composites or crowns?**

   Surface layer staining is possible if silver diamine fluoride flows past the area of contact onto restorations. The stain can be prevented with careful application and by wiping adjacent restorations following application to lesions or high-risk sites. If staining of restorations occur they can be removed with **standard pumice** or cleaning devices.

   Be aware that existing restorations can present with marginal leakage and associated demineralization. If silver diamine fluoride reaches these compromised margins, it is possible for caries arrest and discoloration to occur.

8. **Can I cover a treated and discolored site or excavate on recall appointments?**

   Yes, if Advantage Arrest is used during a diagnostic appointment to arrest active disease, during the restorative visit the treated site can be evaluated for caries arrest providing you and the patient several options. You could choose to 1) reapply SDF, 2) simply leave the site as is, 3) cover the site without anesthetic or excavation or finally 4) excavate the site and place a restoration.

9. **What can you tell me about the use of potassium iodide (KI) to remove or reduce the staining effects of silver diamine fluoride 38%?**

   The use of potassium iodide (KI) has been mentioned when silver diamine fluoride 38% (SDF) is used on a prepared tooth cavity during a restorative procedure in an attempt to limit silver oxides from shadowing through restorative materials. The use of KI has not been recommended when silver diamine fluoride 38% is used as a primary prevention agent, as a stand-alone treatment or with light cured restorative procedures.

   KI binds the silver portion of SDF forming a white precipitate of silver iodide. Repetitive, applications of KI are used to scrub, wash, rinse and repeat on cavity floors and walls in an attempt to remove as much of the silver as possible. Since SDF penetrates lesioned enamel and dentin and tooth defects so quickly not all of the silver can be bound and/or removed. Clinicians have reported, and research confirms, that when they have applied this technique the stain from the residual silver will still oxidize in weeks after treatment and cause shadowing through of any translucent restorative materials.

   Research has shown the use of a KI scrub will remove or bind silver and negatively impact the caries prevention actions of SDF. KI can also affect the bond strength of restorations so additional prep work must be completed around the treatment area to ensure bonding.

   Some findings include:

   Conclusions: It was concluded that if (SDF+KI) is used as a desensitizing and cavity cleaning agent then tooth surfaces should be lightly roughened. (SDF+KI) should not be used as a whole cavity disinfecting agent but may be used for spot application where a cavity floor approximates the pulp where caries-affected dentine may still exist, otherwise adhesion may be compromised.

Effect of a silver diamine fluoride and potassium iodide-based desensitizing and cavity cleaning agent on bond strength to dentine International Jrn. of Adhesion & Adhesives, 68(2016)54–61

Hiroyasu, Koizumi, Hamdi H. Hamama, Michael F. Burrow

10. How can I apply Advantage Arrest to interproximal sites where I suspect carious or incipient lesions?

Practitioners have shared success treating interproximal lesions using tufted or sponged floss soaked with silver diamine fluoride, then pulled into the contact point and left for 60 seconds. Additionally, some clinicians will dry interproximal sites and will wick Advantage Arrest into the contact point from the microbrush applicators without the need for this floss technique.

11. If a tooth surface does not stain from the application of Advantage Arrest is there no preventative effect of the application?

Studies have shown that there is a protective effect to the site of the application of silver diamine fluoride and a halo effect for the entire mouth. References include 83-89 and a systematic review in reference 90.

12. Are there any post appointment instructions for the patient or the caregivers/guardians?

There are no postoperative limitations. Patients may eat or drink immediately. Patients may brush their teeth with fluoridated toothpaste on their regular schedule.

13. What does an arrested lesion treated with SDF look like on radiographs?

Arrested lesions look like a lesion (scar) on radiographs. You will observe only slight increases in radio-opacity as the mineralization of the previously softened dentin increases. Ultimately the best test of arrest is still the color change and tactile hardness of the dentin surface.

It is advised that you educate your referring dentist(s) about your use of Advantage Arrest since the appearance of a treated lesion might be new and confusing for many practitioners.

14. Can SDF be used as a cavity liner?

SDF is cleared in the same FDA category as cavity liners. Although there are no head to head clinical trials comparing SDF to other cavity liners, it has been used successfully in this way.

SDF will not discolor intact enamel or dentin. SDF can discolor demineralized tooth structure brown/black. Some of this discoloration may shadow a restoration or be visible at the margins and can create less than optimal esthetic restorations.

15. Can SDF be used as an Indirect Pulp Cap - D3120?

Yes. SDF will arrest residual decay left during indirect pulp cap and can form secondary dentin due to the basic pH of the liquid. Do not use SDF for direct pulp cap procedures.

16. How far into enamel and dentin does SDF penetrate?

Silver and fluoride penetrate about 25 microns into healthy enamel and 200-300 microns into healthy dentin without discoloration. The fluoride creates calcium fluoride and fluorapatite while silver binds with phosphates and protein structures in the tooth. Clinical experience is showing that SDF will initially penetrate and arrest about 2 to 2.5 millimeters of carious tooth structure and seal off deeper active caries from needed nutrients. These deeper portions can arrest by natural means in time and additional SDF applications may speed this process. Deeper lesions (near the pulp) run a higher risk of failure as naturally arresting areas take time to arrest.

17. Who is allowed to apply SDF in clinical practice in my state?

Each State dental practice act is different. Since SDF is a fluoride-containing product indicated for the control of dentinal hypersensitivity, it often fits into the same rules as fluoride varnishes. Please confirm that within your own state's dental practice acts to determine who can apply and if any specific training is required for hygienists and auxiliaries.

18. How do SDF treated sites appear on various systems sold for the detection and/or visualization of caries?

We know of no research from any current detection devices on the impact of SDF treated sites on device detection abilities/anomalies. If you have one of these devices, we encourage you to ask them what you can expect from the use of SDF in your practice.

Our Experience in this field leads us to the following thoughts;

CariVu® is a trans-illumination device. It shines light through the tooth and looks for shadows (which can be active/inactive decay, cracks or anything that blocks light). We would anticipate the Carivu would see SDF treated sites similar to images of decay.

DiagnoDent® detects porphyrins (byproducts from bacteria) trapped in the tooth. DiagnoDent does not see the tooth itself. We would anticipate DiagnoDent to show lower readings as SDF lowers bacteria levels within lesions.

Spectra® is a blue light, yellow filter caries detector. This uses the tooth's auto-fluorescence to detect decay and anomalies in the tooth. Spectra is also capable of seeing porphyrins. We would anticipate where good images can be acquired, especially near marginal edges, you would notice a lower reading of red fluorescence from the device, indicating a lowering of bacterial activity.

19. Should SDF be light cured?

It is not necessary to light cure after an application of SDF, however, recent in-vitro studies show it may improve efficacy of the product. Light-curing SDF causes the silver to oxidize, which will cause staining of any surface treated with SDF. The stain from light-curing SDF on non-decayed surfaces can be cleaned off easily.

If you are placing a restoration on top of the SDF-treated surface at the same appointment, wait at least 60 seconds to allow the SDF to penetrate the lesion, then light cure the SDF-treated area prior to restorative procedures. This may prevent or reduce the graying of the restoration and allow you the opportunity to further clean or prepare margins to minimize staining.

20. Are Consent Forms available for this treatment?

Yes. You can find consent forms in English, Spanish, Mandarin, Cantonese, Arabic and other languages for download at the following link:

https://sites.google.com/site/jeremyahorst/sdfconsents

Please download, edit, and use as it benefits your patients.

21. Have professional dental organizations released guidelines for use regarding SDF?

Yes. The American Dental Association has released Evidence-based clinical practice guidelines on nonrestorative treatments for carious lesions. These guidelines include SDF recommendations for various clinical cases.

https://ebd.ada.org/en/evidence/guidelines/nonrestorative-treatments-for-caries-lesions

The American Academy of Pediatric Dentistry has also released, "Use of Silver diamine fluoride for Dental Caries Management in Children and Adolescents Including those with Special Health Care Needs."

http://www.aapd.org/media/policies_guidelines/g_sdf.pdf

22. Have there been improvements in gingival health after application?

Yes. Initially clinicians noticed reductions in gingivitis near the sites of application. This prompted several studies to look at the antibacterial, anti-plaque and anti-gingivitis effects that SDF might possess. These studies can be found in the references, numbers: 76-82.

Safety

1. What have been the reported adverse events with the use of silver diamine fluoride worldwide?

Where silver diamine fluoride has been used in other countries there are no reports of adverse effects, outside of patients with an allergy to silver.

2. **Is SDF safe for use in children?**

   One drop of SDF (20 uL) contains as much fluoride as a liter of bottled water at 1 ppm F. Regarding the margin of safety for dosing, a study was conducted for FDA review for market clearance in rats and mice to determine the lethal dose by oral and subcutaneous administration. The worst-case scenario is subcutaneous administration and that lethal dose was found to be 380 mg/kg. One drop (25uL) of 38% silver diamine fluoride (SDF) contains 9.5 mg silver diamine fluoride. Thus, one drop of 38% SDF applied to 10 kg (22 lb.) child would equal 0.95 mg/kg, equal to a four-hundred fold safety margin.

   In setting up protocols for undergraduate application of 38% SDF, the University of California San Francisco set a recommended limit of one drop per 10 kg (22 lb.) per treatment visit, with weekly intervals at most, and recently increased that limit to two drops.

3. **What are the safety implications for application of SDF for a patient that has more than six sites to be treated?**

   The Margin of Safety for the volume of product needed to treat six sites is within 130 times the NOAEL (no-observed-adverse-effect-level). Treating more sites in one visit will likely have little practical impact on patient safety. Like protocols for fluoride varnish application, the suspension for several days of fluoride supplements is advised.

4. **Is SDF application safe for use with pregnant patients?**

   The FDA cleared silver diamine fluoride for marketing as a medical device, not a drug, and it has not been studied in pregnant woman. Based on known toxicological and pharmacological information, SDF is not expected to have adverse effects on pregnant patients. This is equivalent to pregnancy category C for drugs.

5. **Is it safe for children for the provider to place SDF on a site(s) for arresting caries, and fluoride varnish on all teeth for prevention, on the same visit?**

   Yes, since one drop of SDF, enough to treat multiple sites, contains 1/10th the milligrams of fluorine of a 0.5 mL unit-dose package of 5% sodium fluoride (NaF) varnish.

   - One drop of SDF (0.025 mL) plus one package (0.5 mL) of 5% NaF Varnish will deliver 12.5 mg F to the patient.
   - One drop of SDF (0.025 mL) plus one package (0.3 mL) of 2.5% NaF Varnish will deliver 4.51 mg F to the patient
   - One drop of SDF (0.025 mL) makes up only 1.12 mg F of the amounts above.

Precautions

1. Patient exclusions and inclusions?

Do not use silver diamine fluoride on patients:

- With an allergy to silver
- With ulcerative gingivitis or stomatitis
- Without an informed consent
- With a low caries risk, CDT code D 0601
- Near any open wound including exposed pulp (direct pulp caps)

Do use silver diamine fluoride for patients:

- With any non-symptomatic active caries
- With deep caries as an indirect pulp cap
- With any incipient watch spot
- With newly erupted molars
- With any at-risk sites such as: unsealed deep pits and fissures, enamel defects, exposed root surfaces, furcations, food traps and old restoration margins

2. Does SDF discolor skin or oral tissue?

Contact to skin is not harmful but is likely to cause temporary tattooing. The effect is not immediate, rather it will be noticed within hours. The speed of discoloration is accelerated with light contact. The staining will be limited to direct areas of contact and will fade over a period of 24-72 hours. Patients should be protected with bibs and safety glasses as in any clinical procedure. If you believe you have touched the applicator to the skin of a patient, it is good to advise them of possible temporary tattooing.

Contact to oral soft tissue is less likely to cause temporary tattooing, but is still possible. Take care to protect soft tissue with petroleum jelly or cocoa butter when an application is adjacent to gingival tissue (root caries, treatment of restoration margins). Light blanching is also possible from prolonged direct contact but has been reported to be minor and resolves within 1-2 days.

3. Are there any contraindications for the use of SDF for the control of caries?

SDF should not be placed on exposed pulps. Studies have shown that 38% silver diamine fluoride conveys more effective protection against decay in other teeth than fluoride varnish with reduced overall fluoride exposure.

4. Does SDF stain countertops, instruments, clothing etc.?

Yes. When dispensing SDF it is a good idea to use an absorbent material that has a coated bottom like a patient bib under the dappen dish and applicator to avoid contact with metal trays and office countertops. If SDF comes in contact with instruments or countertops wash immediately with water, soap, ammonia or iodine tincture and then rinse thoroughly with water. Sodium hypochlorite (household bleach) can also be used for difficult stains once they set into the surface.

SDF treated sites tend to discolor more rapidly with light curing. Care should be taken when bonding translucent restorative materials in anterior teeth. The use of opaquers is recommended when covering extensive anterior treated sites. Self-cured materials may diminish anterior discoloration issues associated with light curing.

Stains to clothing are permanent. Use an applicator that does not drip the SDF as it passes over the patient to the site of treatment.

Restorative Aspects

1. Can SDF be used on a prepared tooth just prior to restoration cementation?

Yes. Desensitizing agents have been shown to be protective of the pulp when placed on crown preparations to reduce dentin permeability. Advantage Arrest, a desensitizer, has been shown safe to the pulp when placed on exposed dentin. In addition, studies have shown desensitization and efficacy in treating softened dentin before placing direct restorations. Usually, the tooth is first treated with silver diamine fluoride 38%. This provides the benefit of sealing tubules plus the antimicrobial benefits of both silver and fluoride. When SDF is applied at the same appointment as the restoration, graying of the restoration is possible. Graying of the restoration has not been reported when done at separate appointments.

2. Does an SDF treated site compromise the bond strength of glass ionomer (GI), resin-modified glass ionomer (RMGI) or resin composite restorations?

There have been several studies looking at bond strength of composite, resin modified glass ionomers, and glass ionomers used after SDF placement in a preparation. Although some data is conflicting, the majority of data shows that glass ionomer restorations bond strengths are increased after SDF placement followed by a rinse/dry step. Data also suggests that resin modified glass ionomers have approximately the same bond strength with or without SDF application to the preparation. Studies suggest that the bond strength of composites will not be affected when using the total etch bonding procedures, but will be slightly weakened when using the self-etch bonding procedure.

SDF treated sites tend to discolor more rapidly with light curing. Care should be taken when bonding translucent restorative materials in anterior teeth. The use of opaquers is recommended when covering extensive anterior treated sites. Self-cured materials may diminish anterior discoloration issues associated with light curing.

3. How does SDF treatment compare to Atraumatic Restorative Treatment (ART)?

One clinical trial investigated the efficacy of silver diamine fluoride 30% (SDF) in arresting dentin caries in primary molars of preschoolers. The study compared the adverse effects, parental aesthetic perception, anxiety and oral health quality measure of SDF compared to Atraumatic Restorative Treatment (ART).

68 patients were randomized into SDF and ART treatment groups.

The study concluded that SDF requires much less chair time and was found to have similar results as ART in arresting caries lesions, anxiety, adverse events, aesthetic perceptions and quality of life.

This study can be found below on pages 94 - 102.

3. Can SDF be used in conjunction with ART, with SDF as the liner underneath the restoration?

Yes. SDF can be placed in a completed prepared tooth (traditional or Atraumatic methods) as a liner underneath glass ionomer restorations. This can improve the bond, preserve tooth structure and arrest decay under and around the restoration. Standard resin-based insurance codes are applicable for this procedure.

Insurance Coding and Reimbursement

1. How can Advantage Arrest be coded using CDT?

SDF is cleared for dentinal hypersensitivity treatment. That code is:

D9910 – application of desensitizing medicament

Includes in-office treatment for root sensitivity. Typically reported on a "per visit" basis for application of topical fluoride. This code is not used for bases, liners or adhesives under restorations.

On January 1, 2016 a CDT code became effective for the use of SDF or 25% silver nitrate and has had one revision effective January 1, 2018. This code has the addition of "……per tooth" and reads as follows:

D1354 – interim caries arresting medicament application – per tooth

Conservative treatment of an active, non-symptomatic carious lesion by topical application of a caries arresting or inhibiting medicament and without removal of sound tooth structure.

The ADA has provided a guide to report D1354, linked here:

http://www.ada.org/~/media/ADA/Publications/Files/D1354_ ADAGuidetoReportingInterimCariesArrestingMedicamentApplication_v1_2017Jul15.pdf?la=en

D1355 – caries preventive treatment – per tooth

Effective January 1, 2021, this code was developed to address the coding gap for primary preventive use of SDF, povidone iodine, and some other preventive products. Using SDF on a healthy tooth surface, to prevent decay should be documented using this code.

The ADA has provided a guide to report D1355, linked here:

https://www.ada.org/~/media/ADA/Publications/Files/D1355_ADAGuideto ReportingCariesPreventiveMedicamentApplication_v1a_2020Oct.pdf?la=en

2. **Can I use code D1208 – topical application of fluoride- excluding varnish for the application of SDF?**

   It is not recommended that D1208 be used to describe the use of SDF. If no other code describes the function you are providing with SDF, consider:

   D1999 – unspecified preventive procedure by report (and including a report) can also be used to record your patient encounter.

3. **Are third party payers reimbursing for D1354?**

   Yes. Many carriers have already included reimbursement for D1354 within many of their plans. It is common for insurance providers to not reimburse for new codes as they develop usual and customary payment data. We estimate that approximately 30-40% of third-party payors allow D1354 coverage. It is important the new D1354 code is used so providers can see the volume and associated fees to determine future coverage.

4. **Do any state Medicaid plans currently pay for D1354?**

   Yes. We estimate 38 or more states are covering D1354. This number is increasing frequently.

5. **Are third party payers reimbursing for D1355?**

   Not yet. It is common for insurance providers to not reimburse for new codes as they develop usual and customary payment data. It is important the new D1355 code is used so providers can see the volume and associated fees to determine future coverage.

6. **Do any state Medicaid plans currently pay for D1354?**

   Not yet. We hope in the coming months and years coverage will begin as it did with D1354.

7. **Can SDF be used preventively, to arrest active lesions, and Fluoride varnish be applied on the same visit and coded?**

   Yes. Each code is different, requires different use, and does not currently have limitations on use at the same appointment as other codes. Clinicians must decide which teeth need with use of SDF, and if the patient needs a fluoride varnish and code appropriately for what is done.

Advantage Arrest Package Insert

Advantage Arrest
Silver Diamine Fluoride 38%

Professional Tooth Desensitizer

Rx Only

Desensitizing Ingredient: Aqueous Silver DiamineFluoride, 38.3% to 43.2% w/v

Inactive Ingredients: Purified water

Clinical Pharmacology: Product forms insoluble precipitates with calcium or phosphate in the dentinaltubules to block nerve impulses.

Indication and Usage: Treatment of dentinal hypersensi-tivity. For use in adults over the age of 21.

Contraindications: This product is contraindicated in patients with ulcerative gingivitis or stomatitis, or known sensitivity to silver or other heavy-metal ions. Patients with more than six affected sites, patients having had fullmouth gingivectomies and patients showing abnormal skin sensitization in daily circumstances are recom- mended for exclusion.

Warnings: This product is intended for local application only. Not for ingestion. Protect the patient's eyes. Use caution to avoid contact with skin or clothing. In the event of exposure to eyes or skin, flush the area copiouslywith water and immediately seek medical consultation. This product yielded positive cytotoxicity in standard testing.

Precautions for Use:

1). Advantage Arrest does not normally stain enamel orburnished dentin. Advise patients that soft dentin ormargins of composite restorations may be stained. Staining may be reversed by gentle polishing with tincture of iodine (weak iodine solution).

2) Advise patients that air-drying and product application can cause momentary transient pain to hypersensitive areas. Advantage Arrest has not been shown to causepulpal necrosis even when soft dentin is treated.

3) Minimize product contact with gingiva and mucous membrane by using recommended amounts and care-ful application. Advantage Arrest may cause reversibleshort-term irritation. When applying Advantage Arrest to areas near the gingiva, apply petroleum jelly or co- coa butter and use cotton rolls to may be difficult to see, use caution to avoid transfer- ring the material from gloved hands to other surfaces.

Precautions for Handling:

1. Storage Precautions
   1) Store in original packaging in a cool, dark place.
   2) Replace cap immediately after use.
   3) Use as soon as dispensed.
2. Advantage Arrest will stain skin, clothes, counter tops,floors and instruments brown or black. Refer to the following for stain removal:
   1) Skin; wash immediately with water, soap, ammoniaor iodine tincture and then rinse thoroughly with water. Do not use excessive methods in an attemptto remove difficult stains from skin as the stains will eventually fade.
   2) Clothing/Countertops/Floors/Instruments ; use thesame procedures as with stained skin. Difficult stains may be treated with sodium hypochlorite.
3. If Advantage Arrest is dispensed into a separate container, be sure to wash or thoroughly wipe thecontainer clean immediately after use.

Adverse Reactions: Transient irritation of the gingivahas rarely been reported.

Dosage and Administration:

1. Isolate the affected area of the tooth with cotton rolls or protect the gingival tissue of the affected tooth withpetroleum jelly. Alternatively, a rubber dam can be usedto isolate the area.
2. Clean and dry the affected tooth surface.
3. For up to 5 treated sites per patient, dispense 1-2 drops of solution into a disposable dappen dish. Transfer material directly to the tooth surface with an applicator.
4. Air-dry.

If needed, one or two reapplications may be adminis-tered at intervals of one week.

How Supplied: Single 10 mL dropper-bottle containing8 mL of product. Not sterile.

Storage: Do not freeze or expose to extreme heat. Keepin an air-tight container in a dark place.

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Silver Fluoride as a Treatment for Dental Caries

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Abstract

Medical management of caries is a distinct treatment philosophy that employs topical minimally invasive therapies that treat the disease and is not merely prevention. This strategy is justified as an alternative or supplement to traditional care by significant disease recurrence rates following comprehensive operative treatment under general anesthesia. Silver diamine fluoride (SDF) is one agent to enable effective noninvasive treatment. The announcement of breakthrough therapy designation by the Food and Drug Administration (FDA) suggests that SDF may become the first FDA-approved drug for treating caries. Since our systematic review performed in April 2015, 4 clinical trials have been completed, which inform an update to the application protocol and frequency regimen. Suggestions from these studies are to skip the rinsing step due to demonstration of safety in young children, start patients with high disease severity on an intensive regimen of multiple applications over the first few weeks, and continue with semiannual maintenance doses as previously suggested. Breakthroughs in elucidating the impact of SDF on the dental plaque microbiome inform potential opportunities for understanding caries arrest. SDF can be added to the set of evidence-based noninvasive methods to treat caries lesions in primary teeth, such as the Hall crown technique and sealing lesions with accessible margins.

Keywords: caries treatment, silver diamine fluoride, silver nitrate, evidence-based dentistry, topical anti-infective agents, tooth remineralization

Dental caries occurs when dental plaque bacteria ferment dietary sugars into acids that dissolve the tooth. Dental caries is the most prevalent human disease (Murray et al. 2012). More than 90% of adults in the United States have experienced caries (Dye et al. 2015). However, disparities in disease severity and access to care persist between high and low socioeconomic groups.

Treatment of the disease itself is needed: change the bacteria, strengthen the tooth, enhance the saliva, and decrease sugar consumption. Medical models of caries treatment attempt to accomplish these goals with antimicrobials, remineralizing agents, salivary stimulation, and dietary behavior modification. Yet there are no Food and Drug Administration (FDA)–approved drugs for *treating* dental caries. Fluoridated toothpaste is approved by the FDA as an over-the-counter drug for *preventing* dental caries. High-concentration fluoride toothpaste and other fluoride products, including fluoride varnish and silver diamine fluoride, are cleared by the FDA as medical devices for treating tooth sensitivity.

Disease Recurrence following Operative Treatment

Operative approaches (e.g., fillings) are helpful to stop the progression of individual lesions. However, treatment should address the disease as well as existing signs of disease. The incidence of new caries lesions (disease recurrence) following comprehensive operative treatment reflects the success of treatments in stopping the disease process itself. Treatment of all lesions at once is commonly performed for children in the relatively ideal conditions of general anesthesia. Figure 1 summarizes the incidence of new caries lesions following treatment of cavities under general anesthesia (GA; adapted from Twetman and Dhar 2015). After 6 mo, 38% ± 1% of patients have new lesions (mean ± standard deviation; Primosch et al. 2001; Chase et al. 2004; Berkowitz et al. 2011); this rises to 45% ± 32% after 1 y (Zhan et al. 2006; Hughes et al. 2012) and 62% ± 15% after 2 y (Almeida et al. 2000; Foster et al. 2006; Amin et al. 2010). These relapse rates indicate a need for improvements in the care paradigm.

Risk from Advanced Techniques

Young children are increasingly sedated and anesthetized to enable operative treatment (e.g., fillings; Bruen et al. 2016). This approach poses a risk to life. Indeed, a Lexus-Nexus search found that the deaths of 44 children from sedation or general anesthesia to enable dental treatment were reported in the news media between 1980 and 2011 (Lee et al. 2013). Too many have shown up in the news since 2011. Yet there is no mandated public reporting, no mandated reporting from state dental boards to any federal agency, and no national database, so these reports underestimate the real incidence. A more comprehensive report from global data estimates a 1:327,684 risk of death from using general anesthesia for dental treatment

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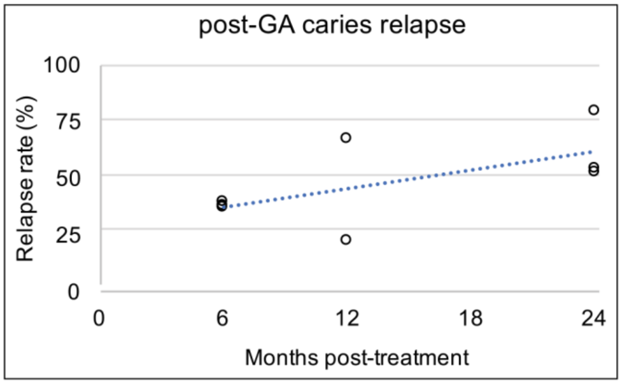

Figure 1. Relapse of signs of dental caries following treatment under general anesthesia (GA). Incidence of new caries lesions following treatment under general anesthesia is plotted against time of evaluation. Linear regression follows y = 1.3x + 29.6, with a correlation coefficient R^2 = 0.4. Adapted from Twetman and Dhar (2015, Table 4). References: Almeida et al. 2000; Primosch et al. 2001; Chase et al. 2004; Foster et al. 2006; Zhan et al. 2006; Amin et al. 2010; Berkowitz et al. 2011; Hughes et al. 2012.

(Mortazavi et al. 2017). It is largely thought that in-office sedation by the operating dentist carries much higher risk, and it has been established that dental specialists carry the greatest risk of negative outcomes for sedation (Coté et al. 2000). Indeed, in a recent survey, over 75% of 439 responding dentists in Virginia said that at least one of their patients had experienced a sedation-related emergency in their offices.

Treatment to Achieve Prevention

Silver diamine fluoride (SDF) is a brush-on liquid that stops 81% of dental caries lesions (Gao, Zhao, et al. 2016). This treatment success rate is similar to that of restorations placed under general anesthesia (Bücher et al. 2014): stopping lesion progress (caries arrest) appears to have the same effect on preventing pain from the lesion as restorations, but these approaches need to be compared directly in diverse clinical situations. In addition, lesion arrest is not the same as the incidence of new lesions (elaborated above for treatment under GA). In that vein, one of the most exciting aspects of SDF is the 58% ± 22% decrease in new lesions after 1 to 3 y compared to no treatment or placebo controls, also outperforming all topical interventions except sealants (Chu et al. 2002; Llodra et al. 2005; Liu et al. 2012; Monse et al. 2012). The effective treatment of caries lesion sensitivity, albeit in the permanent teeth of adults (Castillo et al. 2011), further indicates SDF as an appropriate treatment for caries. SDF meets the goals of decreasing pain and incidence of new lesions.

Stopping Caries Lesion Progression (Caries Arrest)

Three clinical trials on caries arrest by SDF have been published since our systematic review (Fig. 2; Horst et al. 2016). One trial in 3- to 4-y-old children documented a dose-response in both application frequency and concentration (Fung et al. 2016). Twice-annual application resulted in more arrested lesions after 18 mo; similarly, 38% SDF (Saforide; Toyo Seiyaku Kasei Co. Ltd.) stopped more lesions than 12% SDF (Cariostop; Biodinâmica Químicae Farmacêutica LTDA). This trend maintained after 24 and 30 mo, although the magnitude of effect for each regimen appeared to plateau at 18 mo (Fung et al. 2017). The higher effectiveness from increased frequency mimicked that shown previously (Zhi et al. 2012).

Another trial in 3- to 4-y-old children documented increased efficacy at 6 and 12 mo following intensive application (3 times in 2 wk), which was overcome in the single-application group by reapplication at 12 mo (Duangthip et al. 2016). These outcomes support both the concepts of intensive applications at the beginning of treatment and reapplying over longer periods of time. It should be noted that much lower arrest rates were seen in this study than others, which may be explained by the concentration of Cariostop actually having around one-third SDF instead of the advertised 30% (Mei et al. 2013).

A trial in adults averaging 72 y of age showed dramatically more effectiveness in arresting caries, 90% (Li et al. 2016), than the 28% seen in the previous study of arrest in older adults (Zhang et al. 2013). This study also explored the application of potassium iodide (KI) after SDF to reduce discoloration, as the interaction of the 2 produces silver iodide that is yellowish white, instead of black from oxidized silver. This combination did not reduce effectiveness; on the contrary, there was a non-statistically significant trend for higher effectiveness at all timepoints. It may be instructive to note that a similar trend in higher effectiveness at all timepoints was also observed following precipitation with tannic acid (Yee et al. 2009). Unfortunately, using KI did not make a significant change to the discoloration resulting from SDF treatment. Indeed, the intention of applying KI after SDF is to decrease color changes while remaining sealed and blocked from light, as under opaque glass ionomers (personal communication from the inventor, Graham Craig, 2017).

In total, 1,816 patients have been treated with SDF across 12 randomized clinical trials published in English. Pharmacokinetics (Vasquez et al. 2012) and gingival response (Castillo et al. 2011) have been assessed in adults. No significant harms have been noted. This would seem to indicate safety, but in reality, no prospective explicit measure of safety had been published in children. To address this question, we completed a double-blind randomized placebo-controlled superiority trial of SDF in 66 children aged 3 to 5 y. We included a safety questionnaire to parents within 48 h of treatment and physical assessment at follow-up (Milgrom et al. 2017). This "Stopping Cavities" trial documented no adverse events within 21 d after application of blue-tinted SDF (Advantage Arrest; Elevate Oral Care LLC) without a rinse. Higher levels of arrest were observed in this trial (72%), at 2 wk versus the earliest trial outcome of 6 mo (Fig. 2), which suggests that the effect dissipates with time. Concerns have been expressed about losing effectiveness by rinsing SDF away in the UCSF Protocol; the purpose was

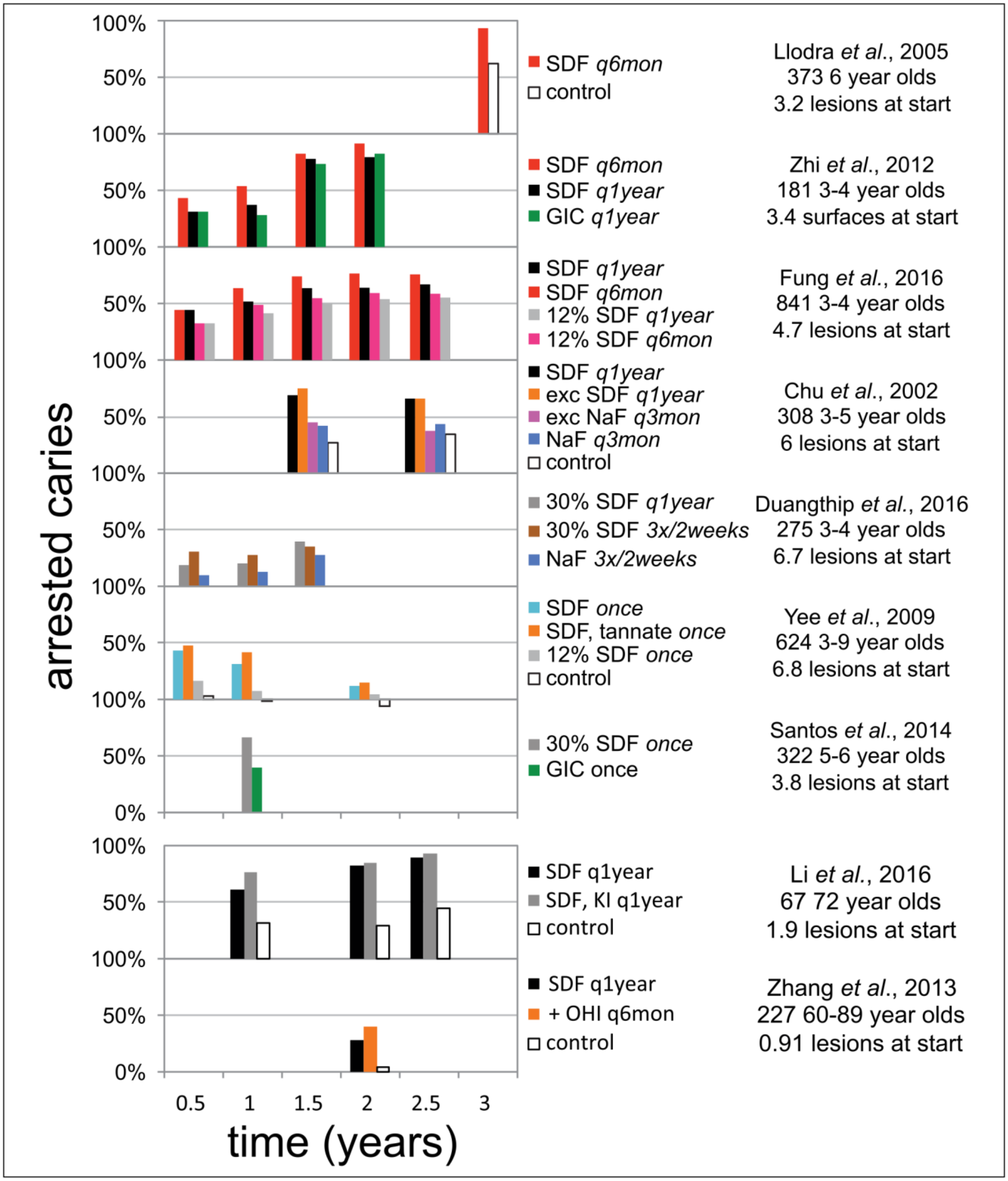

Figure 2. Graphic summary of randomized controlled trials demonstrating caries arrest after topical treatment with silver diamine fluoride (SDF). Studies are arranged vertically by frequency of SDF application. Caries arrest is defined as the fraction of initially active carious lesions that became inactive and firm to a dental explorer. SDF (38% unless noted otherwise); GIC, glass ionomer cement; NaF, 5% sodium fluoride varnish; + OHI q6mon, SDF every year and oral hygiene instructions every 6 mo; q1year, every year; q3mon, every 3 mo; q6mon, every 6 mo. Updated from Horst et al. (2016).

concern of safety without it (Horst et al. 2016). The lack of adverse events observed in this study leaves no apparent reason to continue rinsing lesions after SDF treatment. It is often appropriate to rinse or wipe the tongue only, to remove the taste after SDF application, or to cover the taste by giving the child something with a strong desirable flavor.

From these 4 trials, clinicians may also consider intensive application regimens (e.g., 3 times in 2 wk) and then spreading out further applications over time, skipping the rinse, and further reassurance of a dose-response by application frequency, the need for repeated application over time, and a range from 28% to 90% arrest in treating root caries in older adults.

A recent systematic review found various comparative clinical studies and case series published in Chinese, Japanese, Portuguese, and Spanish (Gao, Zhao, et al. 2016). After excluding studies by quality and risks of bias, they estimated an 81% likelihood of caries arrest in primary teeth (95% confidence interval, 68%–89%) following treatment with 38% SDF regardless of application regimen and duration of evaluation. A recent case series in Oregon showed 100% arrest after 3 mo (Clemens et al. 2017).

Five clinical trials compare caries arrest following treatment with SDF against a control or placebo. In 2 of the studies, the placebo group showed no significant pattern of caries arrest from baseline (Yee et al. 2009; Tan et al. 2010). However, 3 of the studies showed a significant effect, ranging from 34% to 62% of lesions becoming arrested (Chu et al. 2002; Llodra et al. 2005; Li et al. 2016). Thus, it is probable that some lesions do not need treatment and will become arrested without intervention. Consequently, the 81% of caries lesions estimated to arrest following SDF treatment probably include some that would arrest without SDF treatment.

Other Noninvasive Approaches to Arrest Caries

While some medicaments decrease the incidence of new lesions, almost no noninvasive therapies available in the United States have been shown to stop caries lesions in the dentin. Fluoride varnish reverses two-thirds of enamel lesions (Gao, Zhang, et al. 2016) but makes no impact on dentin caries compared to placebo (Chu et al. 2002). While clinical studies during the early and midpart of the past century showed highly inconsistent outcomes from silver nitrate, use to treat dentin caries in the early 1800s and 1900s was common enough to suggest that there is some effect (Black 1908). Sealing in caries, where circumferential enamel is accessible, seems to be the only effective noninvasive alternative (Mertz-Fairhurst et al. 1998).

The Hall crown technique similarly achieves the goal of sealing in caries lesions without removal of any carious material, although the crown margins dive into the gingival sulcus and thus might be considered to have some amount of invasiveness. Nonetheless, the Hall crown does not require accessible cavity margins or removal of any tooth structure. Moreover, clinical outcomes of the Hall technique show superiority to traditional restorations in both comparative clinical trials (Innes et al. 2011; Santamaria et al. 2014).

SDF is the combination of an antimicrobial (Ag, 25% w/v), a remineralizing agent (F, 5%), and a stabilizing agent that happens to also be an antiseptic (ammonia, 8%). As mentioned above, none of the components of SDF have been shown to be consistently effective in treating dentinal caries lesions on their own. This suggests that future gains may be made by further or different combinations.

Regulatory Progress

In 2014, the FDA cleared SDF as a medical device for treating tooth sensitivity. In 2016, the FDA awarded breakthrough therapy status as a commitment to an application for approval of SDF as a drug to treat severe early childhood caries (press release from Elevate Oral Care, October 30, 2016). Breakthrough therapy status does not mean approval; rather, it is a commitment to evaluate and assist in the related new drug application, for a life-threatening disease with no available treatment. Nonetheless, this and the consistent response in many previous clinical trials suggest that SDF will be the first FDA drug to treat dental caries. Canada recently approved SDF with an indication of "anti-caries" (press release from Oral Sciences, March 8, 2017). The Indian Health Service released a policy supporting the use of silver ion antimicrobials (SDF or the combination of silver nitrate and fluoride varnish) in their clinics. The American Dental Association Council on the Advancement of Access and Prevention has written a resolution in support of use of SDF for caries. The American Academy of Pediatric Dentistry has adopted a policy and guideline supporting use to treat caries as well. This wave of support and interest is appropriate given the many large clinical trials that demonstrate effectiveness.

SDF Adoption

Recent conference presentations described studies that document high levels of acceptance of the stains caused by SDF. An elegant study in New York City asked 33 parents to choose between treatment with SDF or white plastic resin fillings, informing them of the considerations to enable these treatments (Tesoriero and Lee 2016). All parents of "uncooperative" children chose SDF, while two-thirds of parents of other children also chose SDF. A sex disparity emerged, wherein 86% of parents chose SDF for their sons, while only 61% chose SDF for their daughters; still, the majority prefer a black stain and uncertainty about outcome over an injection, drill, and prolonged treatment time. The implication is that parents would rather their children have blemishes than experience pain.

Another similar study nearby asked about hypothetical acceptability of the stain. While only 32% of parents accepted the idea of SDF for treating anterior teeth initially, a potential requirement of general anesthesia to enable operative treatment drove acceptance up to 70% (Crystal et al. 2017). It is interesting to consider how responses might have differed if the studies were conducted after the December 2016 FDA Black Box Warning on the use of GA in pregnancy and before the third birthday. Meanwhile, most pediatric dentistry residencies (Nelson et al. 2016) and half of dental school programs are teaching trainees about SDF (Ngoc et al. 2017).

A recent study evaluated the perception of parents whose children were treated with SDF in the case series in Oregon mentioned previously. Most parents strongly agreed that "SDF application is an easy process; I am comfortable with discoloration of cavities after SDF placement; SDF application was pain free for my child; The taste of SDF was acceptable to my child," and all the remaining parents responded as either agreeing or being neutral, except 1 who disagreed about comfort with discoloration (Clemens et al. 2017). Indeed, the first clinical trial of SDF published in English found that parental satisfaction with their children's dental appearance was not different between baseline and 2 y later or between treatment groups. This study in Guangzhou, China, found that 7% of parents described dark teeth as the reason for dissatisfaction, with the remainder concerned about signs of decay in the anterior teeth generally (Chu et al. 2002). This suggests a very high acceptance rate of SDF in cultures as disparate as Guangzhou and Oregon.

SDF Microbial Mechanisms

While considerable in vitro experiments have documented that SDF inactivates every tested protein and bacterium, until the Stopping Cavities trial, no clinical microbiology had been published. The question arose: if SDF kills all bacteria, which microbes are present in the nutrient-rich environment of the SDF-treated caries lesion? To address this question, we performed massively parallel RNA sequencing of a pilot set of plaque samples in the Stopping Cavities trial, taken from 2 caries lesions before and 2 wk after placebo or control treatments for each child (Milgrom et al. 2017). RNA was used as a proxy for vitality, to enable measurement of all vital microbes; RNA degrades within an hour of production in these conditions. Care was taken to minimize inflow of saliva. The hypothesis was that the relative abundance of caries-associated bacteria would be reduced in the treatment group, but surprisingly, no such changes were observed. Mild increases were seen for only a few bacteria not related to caries and that pose no known threat. A trend toward increased diversity was seen, rather than the expected decrease that is ubiquitously observed following a course of systemic antibiotics. This signals safety. Abundant high-quality RNA was retrieved, which was also surprising. The RNA sequences were also scoured for antibiotic or antimetal resistance genes, and these were not changed by treatment. While this was a pilot study in a subset of patients, it is impressive that the microbial composition of the dental plaque on the surface of treated lesions did not significantly change.

Summary

The appropriateness of traditional operative dentistry under sedation and general anesthesia as the first line of treatment for dental caries in primary teeth is in question. The FDA Black Box Warning against general anesthetics in young children urges a paradigm shift. Clearance of SDF in the United States provides an agent for change to noninvasive caries management. Rapid adoption despite the nonesthetic results indicates preference against the discomfort required by traditional operative dentistry, which is further supported by surveys and parent choices. New clinical trial data suggest starting with more frequent applications and decreasing frequency with time, while maintaining at least annual application and removing the rinse step. Our recent work documents a surprising lack of changes to the dental plaque microbiota following SDF treatment. While more work needs to be done to understand and anticipate treatment failure, all new data support the effectiveness and safety for treatment of dental caries by SDF.

Author Contributions

J.A. Horst, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript. The author gave final approval and agrees to be accountable for all aspects of the work.

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Evidence-Based Clinical Practice Guideline on Nonrestorative Treatments for Carious Lesions:
A Report from the American Dental Association

Summary of clinical recommendations for the nonrestorative treatment of caries on **primary teeth**

GRADE Certainty in the Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect.
Low	Our confidence in the effect estimate is limited.
Very Low	We have very little confidence in the effect estimate.

GRADE Interpretation of Strength of Recommendations

Implications	Strong Recommendations	Conditional Recommendations
For Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For Clinicians	Most individuals should receive the intervention.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.
For Policy Makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Before SDF Application

After SDF Application

Expert Panel Recommendation	Certainty in the Evidence	Strength of Recommendation
To arrest advanced cavitated carious lesions on any coronal surface of primary teeth, the expert panel recommends clinicians* prioritize the use of **38% silver diamine fluoride (SDF) solution** (biannual application) over 5% sodium fluoride varnish (application once per week for 3 weeks).†	Moderate	Strong
To arrest or reverse noncavitated carious lesions on occlusal surfaces of primary teeth, the expert panel recommends clinicians* prioritize the use of **sealants + 5% sodium fluoride varnish** (application every 3-6 months) or **sealants alone** over 5% sodium fluoride varnish alone (application every 3-6 months), 1.23% acidulated phosphate fluoride gel (application every 3-6 months), resin infiltration + 5% sodium fluoride varnish (application every 3-6 months), or 0.2% sodium fluoride mouthrinse (once per week).‡	Moderate	Strong
To arrest or reverse noncavitated carious lesions on facial or lingual surfaces of primary teeth, the expert panel suggests clinicians* use **1.23% acidulated phosphate fluoride gel** (application every 3-6 months) or **5% sodium fluoride varnish** (application every 3-6 months).‡	Moderate to Low	Conditional
To arrest or reverse noncavitated carious lesions on approximal surfaces of primary teeth, the expert panel suggests clinicians* use **5% sodium fluoride varnish** (application every 3-6 months), **resin infiltration alone, resin infiltration + 5% sodium fluoride varnish** (application every 3-6 months), or **sealants alone**.‡	Low to Very Low	Conditional
To arrest or reverse noncavitated carious lesions on coronal surfaces of primary teeth, the expert panel suggests clinicians* *do not use* 10% casein phosphopeptide-amorphous calcium phosphate paste if other fluoride interventions, sealants, or resin infiltration is accessible.	Low	Conditional

SDF = silver diamine fluoride

* "Clinicians" refers to the target audience for this guideline, but only those authorized/trained to perform the specified interventions should do so.

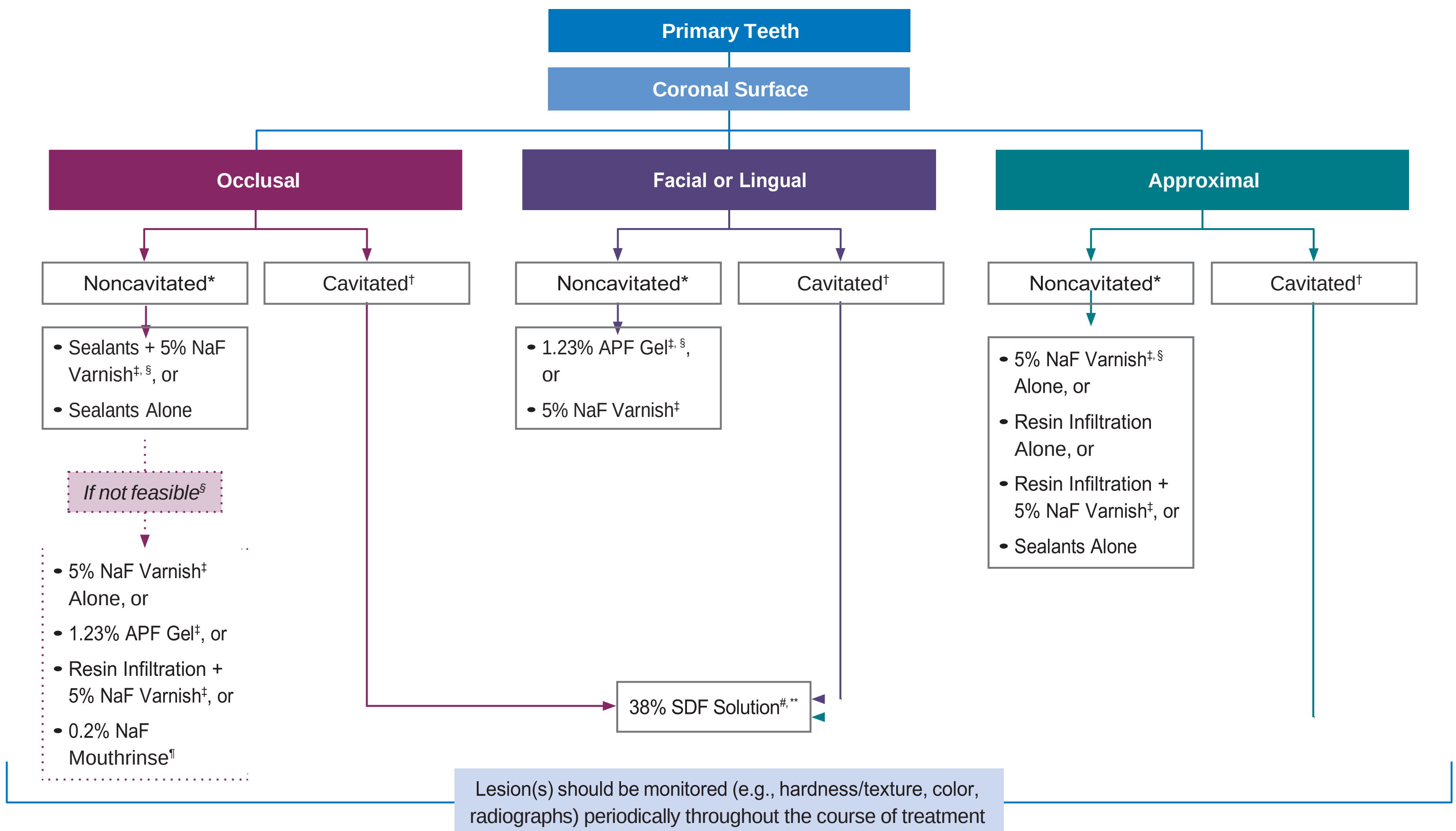
† In keeping with the concept of informed consent, all nonrestorative and restorative treatment options and their potential side effects (such as blackened tooth surfaces treated with silver diamine fluoride) should be offered and explained to all patients.

‡ The order of treatments included in this recommendation represents a ranking of priority defined by the panel when accounting for treatment effectiveness, feasibility, patients' values and preferences, and resource utilization. Considerations such as a particular patient's values and preferences, special needs, or insurance status should inform clinical decision making.

ADA Center for Evidence-Based Dentistry™

Evidence-Based Clinical Practice Guideline on Nonrestorative Treatments for Carious Lesions: A Report from the American Dental Association

Clinical Pathway for the Nonrestorative Treatment of Carious Lesions on **Primary Teeth**



NaF = sodium fluoride
APF = acidulated phosphate fluoride
SDF = silver diamine fluoride

* Defined as International Caries Detection and Assessment System (ICDAS) 1 and 2 lesions.
† Defined as ICDAS 5 and 6 lesions.
‡ Application every 3-6 months.
§ The order of treatments included in this recommendation represents a ranking of priority defined by the panel when accounting for treatment effectiveness, feasibility, patients' values and preferences, and resource utilization. Considerations such as a particular patient's values and preferences, special needs, or insurance status should inform clinical decision making.

¶ At-home use once per week.
\# Biannual application.
**In keeping with the concept of informed consent, all nonrestorative and restorative treatment options and their potential side effects (such as blackened tooth surfaces treated with SDF) should be offered and explained to all patients.

Evidence-Based Clinical Practice Guideline on Nonrestorative Treatments for Carious Lesions:
A Report from the American Dental Association

Summary of clinical recommendations for the nonrestorative treatment of caries on **permanent teeth**

GRADE Certainty in the Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect.
Low	Our confidence in the effect estimate is limited.
Very Low	We have very little confidence in the effect estimate.

GRADE Interpretation of Strength of Recommendations

Implications	Strong Recommendations	Conditional Recommendations
For Patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For Clinicians	Most individuals should receive the intervention.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences.
For Policy Makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

Before SDF Application

After SDF Application

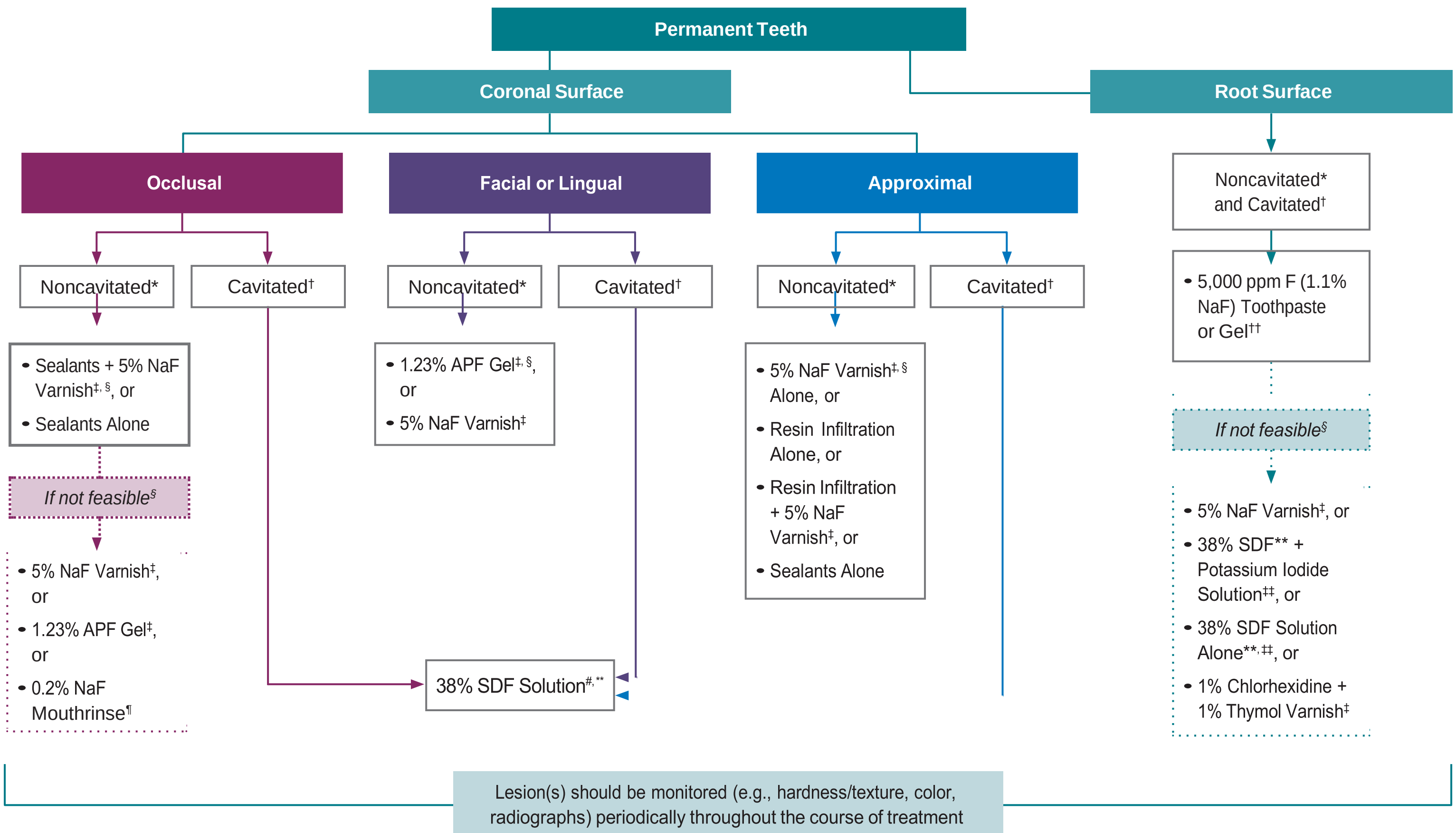
Expert Panel Recommendation	Certainty in the Evidence	Strength of Recommendation
To arrest advanced cavitated carious lesions on any coronal surface of permanent teeth, the expert panel suggests clinicians* prioritize the use of **38% silver diamine fluoride (SDF) solution** (biannual application) over 5% sodium fluoride varnish (application once per week for 3 weeks).[†]	Low	Conditional
To arrest or reverse noncavitated carious lesions on occlusal surfaces of permanent teeth, the expert panel recommends clinicians* prioritize the use of **sealants + 5% sodium fluoride varnish** (application every 3-6 months) or **sealants alone** over 5% sodium fluoride varnish alone (application every 3-6 months), 1.23% acidulated phosphate fluoride gel (application every 3-6 months), or 0.2% sodium fluoride mouthrinse (once per week).[‡]	Moderate	Strong
To arrest or reverse noncavitated carious lesions on facial or lingual surfaces of permanent teeth, the expert panel suggests clinicians* use **1.23% acidulated phosphate fluoride gel** (application every 3-6 months) or **5% sodium fluoride varnish** (application every 3-6 months).[‡]	Moderate to Low	Conditional
To arrest or reverse noncavitated carious lesions on approximal surfaces of permanent teeth, the expert panel suggests clinicians* use **5% sodium fluoride varnish** (application every 3-6 months), **resin infiltration alone**, **resin infiltration + 5% sodium fluoride varnish** (application every 3-6 months), or **sealants alone**.[‡]	Low to Very Low	Conditional
To arrest or reverse noncavitated and cavitated carious lesions on root surfaces of permanent teeth, the expert panel suggests clinicians* prioritize the use of **5,000 ppm fluoride (1.1% sodium fluoride) toothpaste or gel** (at least once per day) over 5% sodium fluoride varnish (application every 3-6 months), 38% SDF + potassium iodide solution (annual application), 38% SDF solution (annual application), or 1% chlorhexidine + 1% thymol varnish (application every 3-6 months).[†,‡]	Low	Conditional
To arrest or reverse noncavitated carious lesions on coronal surfaces of permanent teeth, the expert panel suggests clinicians* *do not use* 10% casein phosphopeptide-amorphous calcium phosphate paste if other fluoride interventions, sealants, or resin infiltration is accessible.	Low	Conditional

SDF = silver diamine fluoride
ppm = parts per million
* "Clinicians" refers to the target audience for this guideline, but only those authorized/trained to perform the specified interventions should do so.
† In keeping with the concept of informed consent, all nonrestorative and restorative treatment options and their potential side effects (such as blackened tooth surfaces treated with silver diamine fluoride) should be offered and explained to all patients.
‡ The order of treatments included in this recommendation represents a ranking of priority defined by the panel when accounting for treatment effectiveness, feasibility, patients' values and preferences, and resource utilization. Considerations such as a particular patient's values and preferences, special needs, or insurance status should inform clinical decision making.

ADA. Center for Evidence-Based Dentistry™

Evidence-Based Clinical Practice Guideline on Nonrestorative Treatments for Carious Lesions: A Report from the American Dental Association

Clinical Pathway for the Nonrestorative Treatment of Carious Lesions on **Permanent Teeth**



NaF = sodium fluoride
APF = acidulated phosphate fluoride
SDF = silver diamine fluoride
ppm = parts per million
F = fluoride

* Defined as International Caries Detection and Assessment System (ICDAS) 1 and 2 lesions.
† Defined as ICDAS 5 and 6 lesions.
‡ Application every 3-6 months.
§ The order of treatments included in this recommendation represents a ranking of priority defined by the panel when accounting for treatment effectiveness, feasibility, patients' values and preferences, and resource utilization. Considerations such as a particular patient's values and preferences, special needs, or insurance status should inform clinical decision making.

¶ At-home use once per week.
\# Biannual application.
** In keeping with the concept of informed consent, all nonrestorative and restorative treatment options and their potential side effects (such as blackened tooth surfaces treated with SDF) should be offered and explained to all patients.
†† At-home use at least once per day.
‡‡ Annual application.

Practice Guidelines

Cover Story

Evidence-based clinical practice guideline on nonrestorative treatments for carious lesions

A report from the American Dental Association

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Supplemental material is available online.

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ABSTRACT

Background. An expert panel convened by the American Dental Association Council on Scientific Affairs and the Center for Evidence-Based Dentistry conducted a systematic review and formulated evidence-based clinical recommendations for the arrest or reversal of noncavitated and cavitated dental caries using nonrestorative treatments in children and adults.

Types of Studies Reviewed. The authors conducted a systematic search of the literature in MEDLINE and Embase via Ovid, Cochrane CENTRAL, and Cochrane database of systematic reviews to identify randomized controlled trials reporting on nonrestorative treatments for noncavitated and cavitated carious lesions. The authors used the Grading of Recommendations Assessment, Development and Evaluation approach to assess the certainty in the evidence and move from the evidence to the decisions.

Results. The expert panel formulated 11 clinical recommendations, each specific to lesion type, tooth surface, and dentition. Of the most effective interventions, the panel provided recommendations for the use of 38% silver diamine fluoride, sealants, 5% sodium fluoride varnish, 1.23% acidulated phosphate fluoride gel, and 5,000 parts per million fluoride (1.1% sodium fluoride) toothpaste or gel, among others. The panel also provided a recommendation against the use of 10% casein phosphopeptide–amorphous calcium phosphate.

Conclusions and Practical Implications. Although the recommended interventions are often used for caries prevention, or in conjunction with restorative treatment options, these approaches have shown to be effective in arresting or reversing carious lesions. Clinicians are encouraged to prioritize use of these interventions based on effectiveness, safety, and feasibility.

Key Words. Carious lesion; American Dental Association; practice guidelines; evidence-based dentistry; decision making; general practice; clinical recommendations; nonrestorative treatments; caries.

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Dental caries is a chronic noncommunicable disease that affects people of all ages worldwide. From 2015 through 2016, approximately 4 of 10 young children[1] and from 2011 through 2012 9 of 10 adults[2] were affected by caries in the United States. Although in the past decade overall caries prevalence has stabilized in both children and adults, these rates remain at a constant high for specific subgroups. According to the 2011-2012 National Health and Nutrition Examination Survey, non-Hispanic white adults aged 20 through 64 years have the highest caries prevalence rates (94%) compared with those of Hispanic, non-Hispanic black, and non-Hispanic Asian adults.[2] The 2015-2016 National Health and Nutrition Examination Survey data show

This article has an accompanying online continuing education activity available at: http://jada.ada.org/ce/home.

that Hispanic youth aged 2 through 19 years also have the highest prevalence rate (52%) compared with non-Hispanic black, non-Hispanic Asian, and non-Hispanic white youth.[1] In addition, there are income-related disparities in caries prevalence in which low-income groups have a higher prevalence of untreated caries than do high-income groups.[1] Worldwide, the direct costs of treatment because of dental disease were estimated to be approximately $298 billion yearly in 2010, with $120 billion attributed to the United States alone.[3]

Caries is caused by frequent acid production from the metabolism of dietary carbohydrates. This mechanism results in the emergence of acid-producing and acid-tolerant organisms in supragingival oral biofilms, altered pH, shift in the demineralization-remineralization equilibrium, and loss of tooth minerals. When there is a balance between protective factors (for example, fluoride, calcium, phosphate, adequate salivary flow, composition) and pathologic factors (for example, cariogenic bacteria, fermentable carbohydrates), demineralization and remineralization of enamel are relatively equal, and oral health is maintained.[4-6]

Preventing the onset of caries across the life span should be the primary goal of a caries management plan. However, once the disease is present, clinicians deal with the challenge of determining the appropriate approach to stop the consequences of the cariogenic process, which can be achieved by applying interventions at the patient level and managing the manifestation of the disease at the lesion level. Patient-level interventions aim to reestablish the mineralization balance. These interventions usually require adequate patient adherence for success and include, but are not limited to, diet counseling (for example, reducing sugar consumption[7]) and oral hygiene instructions and reinforcement[8] (for example, interdental cleaning, toothbrushing with fluoridated toothpaste). Patient-level interventions will be discussed further in a subsequent American Dental Association (ADA) guideline for caries prevention. Lesion-level interventions include nonrestorative or nonsurgical (noninvasive and microinvasive) and restorative or minimally-invasive and invasive treatments. The former are more conservative approaches that stops the disease process through arrest or reversal of carious lesions and minimizes the loss of tooth structure.

Noncavitated carious lesions can be described as surfaces that appear macroscopically intact and without clinical evidence of cavitation.[9] They sometimes are referred to as incipient, initial, early, or white-spot lesions (although these lesions can be white or brown).[10] A cavitated lesion is a carious lesion with a surface that is not macroscopically intact and with a distinct discontinuity or break in the surface integrity, usually determined using visual or tactile means.[9,10] Noncavitated lesions have the potential to reverse by means of chemical interventions or arrest by means of chemical or mechanical interventions. Cavitated lesions are less likely to reverse or arrest without these interventions.

The purpose of this clinical practice guideline is to help clinicians decide which types of nonrestorative treatments or interventions could be used to arrest or reverse existing noncavitated and cavitated carious lesions in adults and children. The target audience for this guideline includes general and pediatric dental practitioners and their support teams, public health dentists, dental hygienists, and community oral health coordinators. Policy makers may also benefit from using this guideline.

This guideline and associated systematic review (O. Urquhart, MPH, written communication, August 2018) are products of an expert panel composed of general, public health, and pediatric dentists and cariologists convened by the ADA Council on Scientific Affairs. Methodological support, stakeholder engagement, and drafting of this clinical practice guideline and its associated systematic review were led by the ADA Center for Evidence-Based Dentistry.

METHODS

We adhered to the Appraisal of Guidelines for Research and Evaluation Reporting Checklist II[11] and Guidelines International Network—McMaster Guideline Development Checklist[12] when developing this guideline and preparing this manuscript. The panelists first met in person to define the scope, purpose, clinical questions, and target audience. Methodologists at the ADA Center for Evidence-Based Dentistry then conducted a systematic review and network meta-analysis of the literature to address the clinical questions (O. Urquhart, MPH, unpublished data, August 2018). At second and third in-person meetings in October 2017 and February 2018 respectively, the panel formulated recommendation statements by using the Grading of Recommendations Assessment, Development and Evaluation evidence to decision framework, facilitated by methodologists at the ADA Center for Evidence-Based Dentistry (O.U., M.P.T., A.C.-L.).[13] This framework involves consideration of a minimum of 4 factors: balance between benefits and harms,

ABBREVIATION KEY

ACP: Amorphous calcium phosphate.
ADA: American Dental Association.
APF: Acidulated phosphate fluoride.
CPP: Casein phosphopeptide.
ICDAS: International Caries Detection and Assessment System.
NaF: Sodium fluoride.
NIDCR: National Institute of Dental and Craniofacial Research.
NIH: National Institutes of Health.
RCT: Randomized controlled trial.
SDF: Silver diamine fluoride.

Table 1. Definition of the certainty in the evidence and strength of recommendations.

DEFINITION OF CERTAINTY (QUALITY) IN THE EVIDENCE*	
Category	**Definition**
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Definition of Strong and Conditional Recommendations and Implications for Stakeholders†		
Implications	**Strong Recommendations**	**Conditional Recommendations**
For Patients	Most people in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help people make decisions consistent with their values and preferences.	Most people in this situation would want the suggested course of action, but many would not.
For Clinicians	Most people should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping people making decisions consistent with their values and preferences.
For Policy Makers	The recommendation can be adapted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.

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certainty in the evidence, patient values and preferences, and resource use. The panel discussed the evidence until reaching consensus. We took the decision to a vote when agreement was elusive. In Grading of Recommendations Assessment, Development and Evaluation, the strength of the recommendations can either be strong or be weak or conditional, and these have different implications for patients, clinicians, and policy makers (Table 1).[14-16] Additional details about the methodology we used to develop this clinical practice guideline are available in the Appendix (available online at the end of this article).

RECOMMENDATIONS

How to use the recommendations

We wrote the recommendations in this clinical practice guideline to assist clinicians, patients, and stakeholders in making evidence-based treatment decisions. Clinical judgment should be used to identify situations in which application of these recommendations may not be appropriate.

Question 1. To arrest cavitated coronal carious lesions on primary or permanent teeth, should we recommend silver diamine fluoride, silver nitrate, or sealants?

Advanced Cavitated Lesions on Any Coronal Tooth Surface

Summary of findings

Four studies (7 reports) including 2,115 participants informed these recommendations.[17-23] After 30 months of follow-up, the use of 38% silver diamine fluoride (SDF) solution applied biannually resulted in a 1.13 times greater chance of arresting advanced cavitated lesions on primary teeth than the use of 38% SDF annually (moderate certainty) and a 1.29 times greater chance of arresting advanced cavitated lesions on primary teeth than the use of 12% SDF solution biannually (high certainty).[18,21,22] In absolute terms, for a population with primary teeth and a 50% chance of arresting or reversing advanced cavitated carious lesions on any coronal surface, 6 more lesions would be arrested or reversed of 100 lesions treated with 38% SDF solution applied biannually compared with 38% SDF solution applied annually after 30 months of follow-up. In addition, after

30 months of follow-up, the use of 30% SDF solution annually resulted in a 1.45 times greater chance of arresting advanced cavitated lesions on primary teeth than the use of 30% SDF solution once per week for 3 weeks and a 1.41 times greater chance of arresting advanced cavitated lesions on primary teeth than 5% sodium fluoride (NaF) varnish applied once per week for 3 weeks (high certainty for both comparisons).[19,20] On average, after 24 months of follow-up, 38% SDF solution applied once at baseline resulted in significantly more advanced cavitated lesions on primary teeth arrested than results with no treatment (mean difference: 1.20, 95% confidence interval [CI] 0.49 to 1.91); this was not the case when 12% SDF solution was applied once at baseline and compared with no treatment.[17] We found no evidence on the effect of silver nitrate or sealants for cavitated lesions on coronal tooth surfaces. eTables 1 and 2[17-23] (available online at the end of this article) and the Appendix (available online at the end of this article) provide a complete report of the results.

Recommendations

- To arrest advanced cavitated carious lesions on any coronal surface of primary teeth, the expert panel recommends clinicians prioritize the use of 38% SDF solution (biannual application) over 5% NaF varnish (application once per week for 3 weeks). (Moderate-certainty evidence, strong recommendation.)
- To arrest advanced cavitated carious lesions on any coronal surface of permanent teeth, the expert panel suggests clinicians prioritize the use of 38% SDF solution (biannual application) over 5% NaF varnish (application once per week for 3 weeks). (Low-certainty evidence, conditional recommendation.)

Remarks

- Although investigators in all included studies assessed the effectiveness of SDF in children with primary teeth, the expert panel did not expect SDF to have a substantially different effect when applied on coronal surfaces of permanent teeth. For this reason, the panel provided a strong recommendation for the use of 38% SDF solution in primary teeth and a conditional recommendation for its use on coronal surfaces of permanent teeth given that there is no direct evidence available informing the effectiveness of any concentration of SDF in permanent teeth (serious issues of indirectness).
- Although SDF has been used in other countries for decades, it was just introduced into the United States in 2014, when the US Food and Drug Administration approved the use of SDF to treat hypersensitivity in adults. At the time of publication, 38% SDF solution is the only concentration available in the United States.[24]
- SDF could be used for a broad range of situations, including, but not limited to, when local or general anesthesia is not preferred, when a patient is not able to cooperate with treatment, or when it is necessary to offer a less costly or less invasive alternative.
- Data suggest that SDF may be more effective on anterior teeth than on posterior teeth. Hypotheses to explain this include, but are not limited to, anterior teeth being easier to keep clean and technique-related challenges for posterior teeth (for example, it is easier to maintain a dry field in the anterior teeth).
- One study informed the effect of SDF on International Caries Detection and Assessment System (ICDAS) 3 and 4 lesions, which involved using visual evaluation (with no radiographic assessment) to measure the progression of these lesions to ICDAS 5 and 6.[19] Although the investigators reported results for approximal, occlusal, and facial or lingual surfaces combined, the panel remains uncertain about the effect of SDF on ICDAS 3 and 4 lesions on each of these surfaces separately. We suggest investigators in future studies use a combination of diagnostic strategies (for example, radiographic assessment and visual evaluation) for this type of lesion.
- Hardness of tooth surfaces on probing is an indication that a lesion is arrested. In contrast, the color of the lesion (that is, black) is not an acceptable method to judge arrest of a lesion.
- An adverse effect associated with SDF is black staining of the lesion, which may not be acceptable to some patients, parents, or caregivers.[25]
- In keeping with the concept of informed consent, clinicians should offer or explain all nonsurgical and restorative treatment options and their potential adverse effects (such as blackened tooth surfaces treated with SDF) to all patients.

Question 2. To arrest or reverse noncavitated coronal carious lesions on primary or permanent teeth, should we recommend NaF, stannous fluoride, acidulated phosphate fluoride (APF), difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, amorphous calcium phosphate (ACP), casein phosphopeptide (CPP)–ACP, nano-hydroxyapatite, tricalcium phosphate, or prebiotics with or without 1.5% arginine, probiotics, SDF, silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, or carbamide peroxide?

Noncavitated Lesions on Occlusal Surfaces

Summary of findings

Eight studies including 726 participants informed these recommendations.[26-33] Noncavitated occlusal lesions treated with sealants plus 5% NaF varnish,[28,32] sealants alone,[29-31] 5% NaF varnish alone,[28,31-33] 1.23% APF gel,[26] resin infiltration plus 5% NaF varnish,[28] or 0.2% NaF mouthrinse plus supervised toothbrushing[31] had a 2 to 3 times greater chance of being arrested or reversed than results with no treatment (moderate certainty for all comparisons). The combination of sealants plus 5% NaF varnish[28,32] was the most effective at arresting or reversing noncavitated occlusal lesions. eTable 3 (available online at the end of this article) and the Appendix (available online at the end of this article) provide a complete report of the results.

Recommendations

- To arrest or reverse noncavitated carious lesions on occlusal surfaces of primary teeth, the expert panel recommends clinicians prioritize the use of sealants plus 5% NaF varnish (application every 3-6 months) or sealants alone over 5% NaF varnish alone (application every 3-6 months), 1.23% APF gel (application every 3-6 months), resin infiltration plus 5% NaF varnish (application every 3-6 months), or 0.2% NaF mouthrinse (once per week). (Moderate-certainty evidence, strong recommendation.)
- To arrest or reverse noncavitated carious lesions on occlusal surfaces of permanent teeth, the expert panel recommends clinicians prioritize the use of sealants plus 5% NaF varnish (application every 3-6 months) or sealants alone over 5% NaF varnish alone (application every 3-6 months), 1.23% APF gel (application every 3-6 months), or 0.2% NaF mouthrinse (once per week). (Moderate-certainty evidence, strong recommendation.)

Remarks

- The order of treatments included in this recommendation is a ranking of priority that the panel defined when accounting for their effectiveness, feasibility, patient values and preferences, and resource use.
- The panel prioritized the use of sealants plus 5% NaF varnish or sealants alone over the use of all other treatments for occlusal noncavitated lesions on both primary and permanent teeth. Although the studies in which the investigators examined the combination of sealants plus 5% NaF were conducted in primary teeth, the panel had no reason to believe these treatments would have a substantially different effect when applied to permanent teeth.
- Investigators in the studies informing the recommendations for sealants included a mixture of resin-based, glass ionomer cement, and resin-modified glass ionomer sealants and reported a range in sealant retention from 41% through 89%. Maintaining a dry field and using proper technique are essential for sealant effectiveness and retention. If maintaining a dry field is not possible, a hydrophilic sealant material such as glass ionomer cement may be preferred over resin-based material.[34] In settings in which the quality of sealant application cannot be guaranteed, the panel suggests that clinicians consider other treatments included in the recommendations. Notably, enamel removal is unnecessary before sealant application.
- The study[31] in which the investigators provided data about 0.2% NaF mouthrinse also included supervised toothbrushing as a co-intervention.
- Although data from 1 study[28] support the use of resin infiltration plus 5% NaF varnish on occlusal surfaces of primary teeth, resin infiltration has been developed and studied primarily for treating approximal surfaces. The panel advises clinicians to consider the relatively high costs associated with this intervention compared with the cost of sealants.
- To mitigate the risk of experiencing accidental ingestion of high doses of fluoride, 0.2% NaF mouthrinses are not appropriate for uncooperative children who cannot control swallowing. In addition, in-office gels (for example, 1.23% APF gel) require suction to minimize swallowing, especially when used in children.

Noncavitated Lesions on Approximal Surfaces

Summary of findings

Thirteen studies (14 reports) including 2,516 participants informed these recommendations.[35-48] Noncavitated approximal carious lesions treated with the combination of resin infiltration plus 5% NaF varnish[42] had a 5 times greater chance of being arrested or reversed than results with no treatment (very low certainty). When either resin infiltration[45,47,48] or sealants[43-46] were used without another agent, there was a 2 times greater chance of arrest or reversal than results with no treatment (low certainty for both comparisons). Finally, when only 5% NaF varnish[42,43] was used, there was a 2 times greater chance of arrest or reversal; however, these results were not statistically significant (very low certainty). eTable 4 (available online at the end of this article) and the Appendix (available online at the end of this article) provide a complete report of the results.

Recommendation

- To arrest or reverse noncavitated carious lesions on approximal surfaces of primary and permanent teeth, the expert panel suggests clinicians use 5% NaF varnish (application every 3-6 months), resin infiltration alone, resin infiltration plus 5% NaF varnish (application every 3-6 months), or sealants alone. (Low- to very-low-certainty evidence, conditional recommendation.)

Remarks

- The order of treatments included in this recommendation is a ranking of priority that the panel defined when accounting for their effectiveness, feasibility, patient values and preferences, and resource use.
- After detecting an approximal lesion (and when it is not possible or feasible to separate the teeth for direct clinical observation), the clinician must rely on radiographic depth to diagnose the lesion as noncavitated or cavitated. Study investigators included lesions with radiolucencies ranging from the enamel to lesions in the outer one-third of the dentin. The panel emphasizes that approximal lesions that appear limited to the enamel and outer one-third of the dentin on radiographs are most likely noncavitated, and the clinician should prioritize the use of nonrestorative interventions.[49]
- Investigators in the studies informing the use of resin infiltration alone conducted the studies in permanent teeth,[45,47] whereas the study investigators examining the use of resin infiltration plus 5% NaF varnish conducted the study in primary teeth.[42] Investigators in 1 study[35] examined the effectiveness of resin infiltration in mixed dentition, and the results suggested that it was significantly more effective in arresting or reversing approximal noncavitated lesions than was the control, described by the investigators as "mock treatment." The panel suggested using these treatments in both primary and permanent teeth because they did not expect them to have a substantially different effect in the 2 types of dentition. Resin infiltration is technique sensitive and may not be appropriate for uncooperative children.
- The evidence supporting the recommendation for sealants on approximal surfaces came from studies in which the investigators evaluated resin-based and glass ionomer cement sealants.[41,43-46] In no included studies did the investigators report on sealant retention for approximal surfaces. In addition, the use of sealants on approximal surfaces requires temporary tooth separation (a few days) and is technique sensitive. The remarks associated with the use of sealants on occlusal surfaces also apply to the use of sealants on approximal surfaces.

Noncavitated Lesions on Facial or Lingual Surfaces

Summary of findings

Five studies including 584 participants informed this recommendation.[26,33,50-52] Noncavitated facial or lingual carious lesions treated with 5% NaF varnish[33] had a 2 times greater chance of being arrested or reversed than results with no treatment (low certainty), whereas those treated with 1.23% APF gel[26] also had a 2 times greater chance of being arrested or reversed than results with oral health education (moderate certainty). When investigators compared 10% CPP-ACP[52] with placebo cream, the results suggested that it may increase the chance of arresting or reversing lesions; however, these results were neither statistically nor clinically significant (low certainty). eTables 5 and 6 (available online at the end of this article) and the Appendix (available online at the end of this article) provide a complete report of the results.

Recommendation

- To arrest or reverse noncavitated carious lesions on facial or lingual surfaces of primary and permanent teeth, the expert panel suggests clinicians use 1.23% APF gel (application every 3-6 months) or 5% NaF varnish (application every 3-6 months). (Moderate- to low-certainty evidence, conditional recommendation.)

Remarks

- The order of treatments included in this recommendation is a ranking of priority that the panel defined when accounting for their effectiveness, feasibility, patient values and preferences, and resource use.
- In-office gels (for example, 1.23% APF gel) require suction to minimize swallowing, especially when used in uncooperative children.

Noncavitated Lesions on Any Coronal Tooth Surface

Summary of findings

Seven studies including 2,365 participants informed this recommendation.[26,33,53-57] Among studies in which the investigators reported data for all coronal surfaces combined, noncavitated carious lesions treated with 5% NaF varnish (low certainty)[33] and 1.23% APF gel (moderate certainty)[26] had a 2 times greater chance of being arrested or reversed than results with no treatment. Although 10% CPP-ACP[57] may increase the chance of arrest or reversal by 3%, these results were neither statistically nor clinically significant (low certainty). eTable 7 (available online at the end of this article) and the Appendix (available online at the end of this article) provide a complete report of the results.

Recommendation

- To arrest or reverse noncavitated carious lesions on coronal surfaces of primary and permanent teeth, the expert panel suggests clinicians do not use 10% CPP-ACP if other fluoride interventions, sealants, or resin infiltration is accessible. (Low-certainty evidence, conditional recommendation.)

Remark

- The panel emphasizes that 10% CPP-ACP should not be used as a substitute for fluoride products.

We found no evidence on the effect of stannous fluoride, difluorsilane, ammonium fluoride, calcium phosphate, ACP, nano-hydroxyapatite, tricalcium phosphate, or prebiotics with or without 1.5% arginine, SDF, silver nitrate, lasers, sodium bicarbonate, calcium hydroxide, or carbamide peroxide for noncavitated lesions on any coronal tooth surface.

Question 3. To arrest cavitated root carious lesions or arrest or reverse noncavitated root carious lesions on permanent teeth, should we recommend NaF, stannous fluoride, APF, difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, ACP, CPP-ACP, nano-hydroxyapatite, tricalcium phosphate, or prebiotics with or without 1.5% arginine, probiotics, SDF, silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, or carbamide peroxide?

Noncavitated and Cavitated Lesions on Root Surfaces

Summary of findings

Eight studies including 584 participants informed these recommendations.[58-65] Noncavitated and cavitated root carious lesions treated with 5,000 parts per million fluoride (1.1% NaF) toothpaste or gel[60-62,64] had a 3 times greater chance of arrest or reversal than results with no treatment (low certainty). The use of 1% chlorhexidine plus thymol varnish,[59] 38% SDF solution applied annually,[63] 38% SDF plus potassium iodide[63] applied annually, or 5% NaF varnish[65] also had a 2 to 3 times greater chance of arrest or reversal; however, these results were not statistically significant (very low certainty). We found no evidence on the effect of stannous fluoride, APF, ammonium fluoride, polyols, calcium phosphate, ACP, CPP-ACP, nano-hydroxyapatite, tricalcium phosphate, or prebiotics with or without 1.5% arginine, probiotics, silver nitrate, lasers, resin infiltration, sealants,

Table 2. Summary of clinical recommendations for the nonrestorative treatment of caries.

CLINICAL QUESTION	PRIMARY DENTITION RECOMMENDATIONS	PERMANENT DENTITION RECOMMENDATIONS
To arrest cavitated coronal carious lesions on primary or permanent teeth, should we recommend SDF,* silver nitrate, or sealants?	To arrest advanced cavitated carious lesions on any coronal surface of primary teeth, the expert panel recommends clinicians† prioritize the use of 38% SDF solution (biannual application)‡ over 5% NaF§ varnish (application once per week for 3 weeks) (certainty: moderate; strength: strong).	To arrest advanced cavitated carious lesions on any coronal surface of permanent teeth, the expert panel suggests clinicians prioritize the use of 38% SDF solution (biannual application)‡ over 5% NaF varnish (application once per week for 3 weeks) (certainty: low; strength: conditional).
To arrest or reverse noncavitated coronal carious lesions on primary or permanent teeth, should we recommend NaF, stannous fluoride, APF,¶ difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, ACP,# CPP-ACP, nano-hydroxyapatite, tricalcium phosphate, or prebiotics with or without 1.5% arginine, probiotics, SDF, silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, or carbamide peroxide?**	To arrest or reverse noncavitated carious lesions on occlusal surfaces of primary teeth, the expert panel recommends clinicians prioritize the use of sealants plus 5% NaF varnish (application every 3-6 months) or sealants alone over 5% NaF varnish alone (application every 3-6 months), 1.23% APF gel (application every 3-6 months), resin infiltration plus 5% NaF varnish (application every 3-6 months), or 0.2% NaF mouthrinse (once per week) (certainty: moderate; strength: strong).††	To arrest or reverse noncavitated carious lesions on occlusal surfaces of permanent teeth, the expert panel recommends clinicians prioritize the use of sealants plus 5% NaF varnish (application every 3-6 months) or sealants alone over 5% NaF varnish (application every 3-6 months), 1.23% APF gel (application every 3-6 months), or 0.2% NaF mouthrinse (once per week) (certainty: moderate; strength: strong).††
	To arrest or reverse noncavitated carious lesions on approximal surfaces of primary teeth, the expert panel suggests clinicians use 5% NaF varnish (application every 3-6 months), resin infiltration alone, resin infiltration plus 5% NaF varnish (application every 3-6 months), or sealants alone (certainty: low to very low; strength: conditional).††	To arrest or reverse noncavitated carious lesions on approximal surfaces of permanent teeth, the expert panel suggests clinicians use 5% NaF varnish (application every 3-6 months), resin infiltration alone, resin infiltration plus 5% NaF varnish (application every 3-6 months), or sealants alone (certainty: low to very low; strength: conditional).††
	To arrest or reverse noncavitated carious lesions on facial or lingual surfaces of primary teeth, the expert panel suggests clinicians use 1.23% APF gel (application every 3-6 months) or 5% NaF varnish (application every 3-6 months) (certainty: moderate to low; strength: conditional).††	To arrest or reverse noncavitated carious lesions on facial or lingual surfaces of permanent teeth, the expert panel suggests clinicians use 1.23% APF gel (application every 3-6 months) or 5% NaF varnish (application every 3-6 months) (certainty: moderate to low; strength: conditional).††
	To arrest or reverse noncavitated carious lesions on coronal surfaces of primary teeth, the expert panel suggests clinicians do not use 10% CPP-ACP paste if other fluoride interventions, sealants, or resin infiltration is accessible (certainty: low; strength: conditional).	To arrest or reverse noncavitated carious lesions on coronal surfaces of permanent teeth, the expert panel suggests clinicians do not use 10% CPP-ACP paste if other fluoride interventions, sealants, or resin infiltration is accessible (certainty: low; strength: conditional).
To arrest cavitated root carious lesions or arrest or reverse noncavitated root carious lesions on permanent teeth, should we recommend NaF, stannous fluoride, APF, difluorsilane, ammonium fluoride, polyols, chlorhexidine, calcium phosphate, ACP, CPP-ACP, nano-hydroxyapatite, tricalcium phosphate, or prebiotics with or without 1.5% arginine, probiotics, SDF or silver nitrate, lasers, resin infiltration, sealants, sodium bicarbonate, calcium hydroxide, or carbamide peroxide?	Not applicable	To arrest or reverse noncavitated and cavitated carious lesions on root surfaces of permanent teeth, the expert panel suggests clinicians prioritize the use of 5,000 parts per million fluoride (1.1% NaF) toothpaste or gel (at least once per day) over 5% NaF varnish (application every 3-6 months), 38% SDF plus potassium iodide solution (annual application), 38% SDF solution (annual application), or 1% chlorhexidine plus 1% thymol varnish (application every 3-6 months) (certainty: low; strength: conditional).††

* SDF: Silver diamine fluoride. † *Clinicians* refers to the target audience for this guideline, but only those authorized or trained to perform the specified interventions should do so. ‡ In keeping with the concept of informed consent, clinicians should offer or explain all nonsurgical and restorative treatment options and their potential adverse effects (such as blackened tooth surfaces treated with SDF) to all patients. § NaF: Sodium fluoride. ¶ APF: Acidulated phosphate fluoride. # ACP: Amorphous calcium phosphate. ** CPP: Casein phosphopeptide. †† The order of treatments included in this recommendation represents a ranking of priority defined by the panel when accounting for treatment effectiveness, feasibility, patients' values and preferences, and resource utilization. Considerations such as a particular patient's values and preferences, special needs, or insurance status should inform clinical decision making.

sodium bicarbonate, calcium hydroxide, or carbamide peroxide for cavitated or noncavitated lesions on root surfaces. eTable 8[58-65] (available online at the end of this article) and the Appendix (available online at the end of this article) provide a complete report of the results.

Recommendation

- To arrest or reverse noncavitated and cavitated carious lesions on root surfaces of permanent teeth, the expert panel suggests clinicians prioritize the use of 5,000 ppm fluoride (1.1% NaF) toothpaste or gel (at least once per day) over 5% NaF varnish (application every 3-6 months), 38% SDF plus potassium iodide solution (annual application), 38% SDF solution (annual

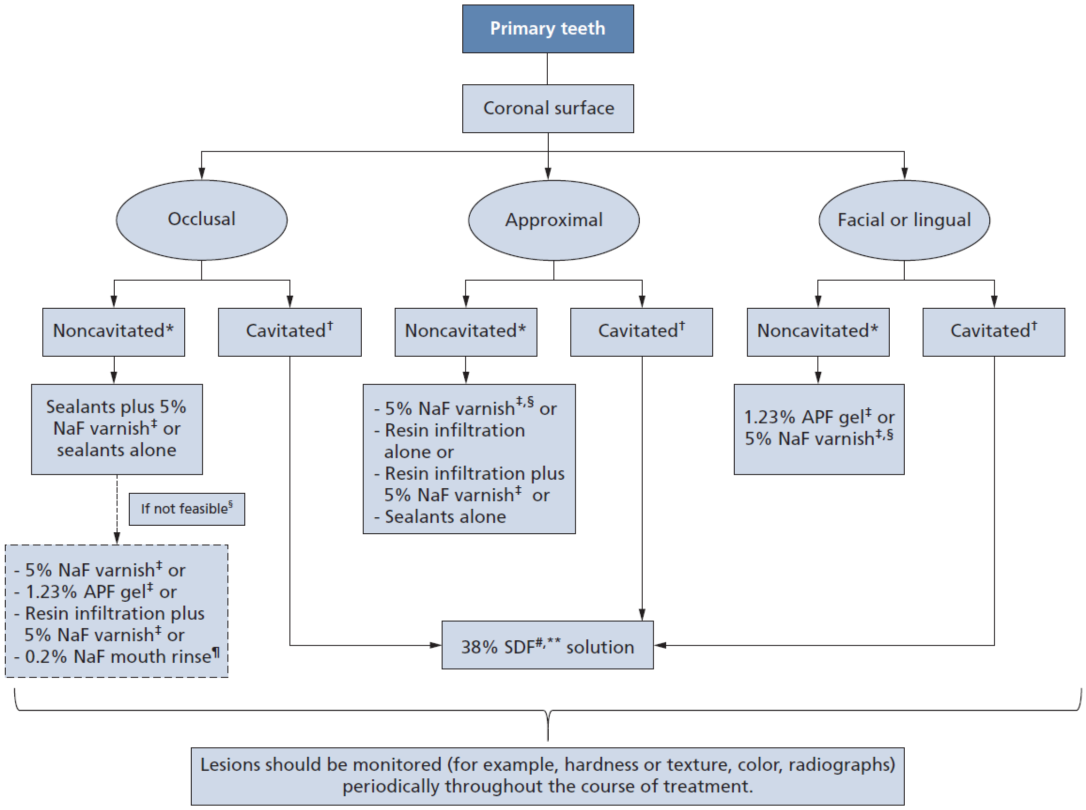

Figure 1. Clinical pathway for the nonrestorative treatment of noncavitated and cavitated carious lesions on primary teeth. APF: Acidulated phosphate fluoride. NaF: Sodium fluoride. SDF: Silver diamine fluoride. * Defined as ICDAS 1-2. † Defined as ICDAS 5-6. ‡ Application every 3 through 6 months. § The order of treatments included in this recommendation represents a ranking of priority defined by the panel when accounting for treatment effectiveness, feasibility, patients' values and preferences, and resource utilization. Considerations such as a particular patient's values and preferences, special needs, or insurance status should inform clinical decision making. ¶ At-home use once per week. # Biannual application. ** In keeping with the concept of informed consent, all nonsurgical and restorative treatment options and their potential side effects (such as blackened tooth surfaces treated with SDF) should be offered and explained to all patients.

application), or 1% chlorhexidine plus 1% thymol varnish (application every 3-6 months). (Low-certainty evidence, conditional recommendation.)

Remarks

- The order of treatments included in this recommendation is a ranking of priority that the panel defined by accounting for their effectiveness, feasibility, patient values and preferences, and resource use.
- Given that noncavitated and cavitated root lesions are difficult to distinguish in practice, the panel did not provide separate recommendations for these 2 types of lesions.
- Investigators conducted all studies in adult or older adult patients (permanent teeth), who are predominantly affected by root caries.
- The use of 5,000 ppm fluoride (1.1% NaF) toothpaste or gel requires patient adherence, which includes filling prescriptions and daily use at home. Because adherence is integral to its success, this intervention may not be feasible for populations in nursing homes and those with special needs. Furthermore, this treatment may not be covered universally by insurance. At the time of publication, some brand-name toothpastes cost 23 cents per toothbrushing, and generic versions cost 17 cents per toothbrushing.[66] If cost is a barrier, other interventions suggested for treating root caries may be more appropriate. Finally, if 38% SDF solution is chosen over 5,000 ppm fluoride (1.1% NaF) toothpaste or gel, the remarks associated with the use of SDF for cavitated lesions on any coronal surface also apply to the use of SDF on root surfaces.

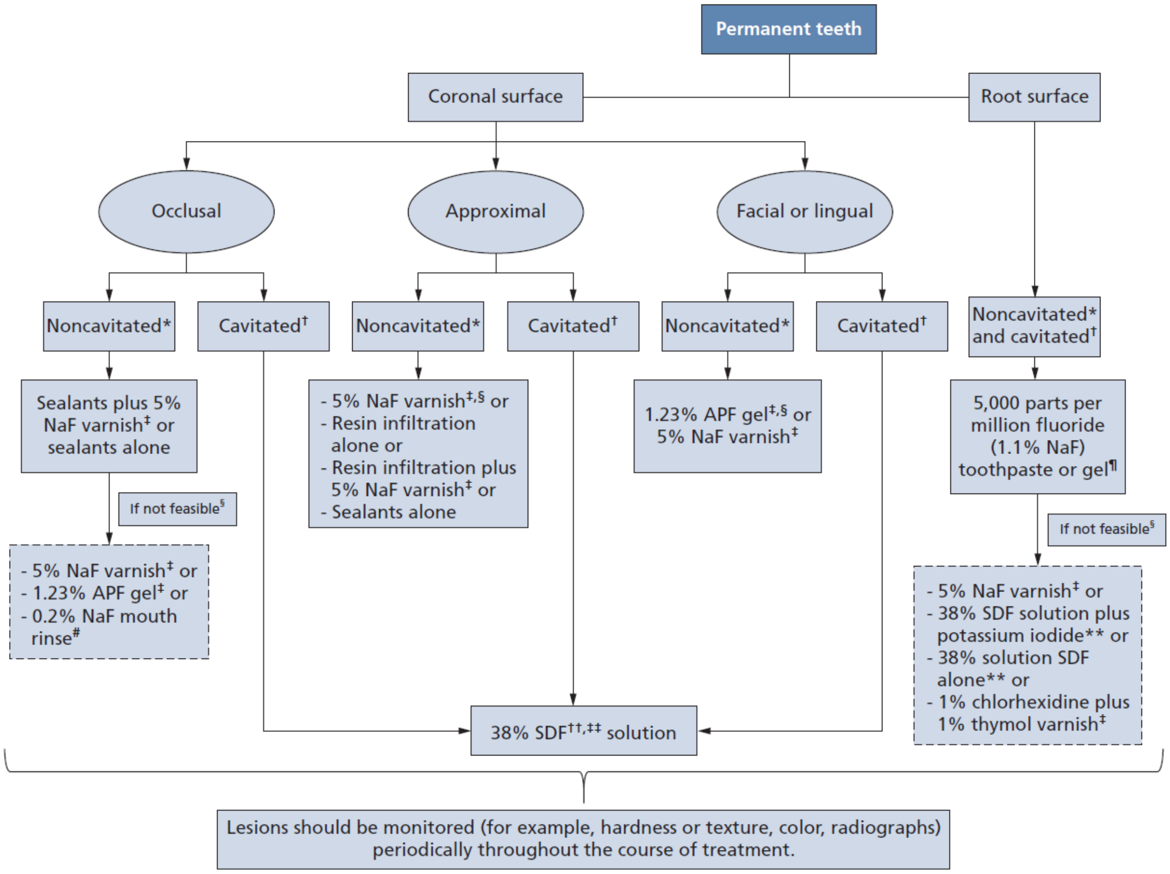

Figure 2. Clinical pathway for the nonrestorative treatment of noncavitated and cavitated carious lesions on permanent teeth. APF: Acidulated phosphate fluoride. NaF: Sodium fluoride. SDF: Silver diamine fluoride. * Defined as ICDAS 1-2. † Defined as ICDAS 5-6. ‡ Application every 3 to 6 months. § The order of treatments included in this recommendation represents a ranking of priority defined by the panel when accounting for treatment effectiveness, feasibility, patients' values and preferences, and resource utilization. Considerations such as a particular patient's values and preferences, special needs, or insurance status should inform clinical decision making. # At-home use once per week. †† Biannual application. ¶ At-home use at least once per day. ** Annual application. ‡‡ In keeping with the concept of informed consent, all nonsurgical and restorative treatment options and their potential side effects (such as blackened tooth surfaces treated with SDF) should be offered and explained to all patients.

Table 2 provides information about all recommendations, certainty in the evidence, and strength of recommendations. Figures 1 and 2 illustrate the recommendation statements as an algorithm. A For the Patient page accompanies this guideline and will help clinicians communicate these recommendations to their patients.[67]

DISCUSSION

Implications for practice

This clinical practice guideline is the first in a series on caries management and includes evaluation of only nonrestorative treatments for existing lesions. Other articles in this series will provide guidance on caries prevention, caries detection and diagnosis, and restorative treatments. Many of the interventions included in this guideline's recommendations also are used regularly for caries prevention or as part of restorative treatment and will be reviewed again in those articles. Furthermore, the recommendations included in this article will be contextualized fully once all articles in the series are published and recommendations are collated.

Clinicians can use a variety of treatments to arrest or reverse carious lesions. We approached decision making by considering the type of lesion (noncavitated or cavitated), dentition (primary or permanent), and tooth surface (for example, occlusal). The certainty in the evidence informing our recommendations ranged from very low to high because of issues of risk of bias, imprecision, indirectness, and inconsistency.[16]

The expert panel emphasizes the importance of actively monitoring noncavitated and cavitated lesions during the course of nonrestorative treatment to ensure the success of the management plan. Clinicians should observe signs of hardness on gentle probing or radiographic evidence of arrest or reversal over time and, if they do not see these signs, should implement additional or alternative treatment options. The panel suggests applying all treatments according to the dosage and technique provided within manufacturers' instructions.

Finally, although we did not include diet counseling as an intervention in this guideline, the panel emphasizes that nonrestorative treatments should be accompanied by a diet low in sugar.[68] The panel will consider dietary modifications as an intervention for the next article on caries prevention.

Implications for research

We urge researchers to conduct high-quality randomized controlled trials (RCTs) on nonrestorative treatments included in this guideline, especially for interventions for which there are a lack of RCTs. We also emphasize the importance of improving the reporting quality of primary studies.

Although high-quality RCTs in which the investigators evaluate the effect of SDF on advanced cavitated coronal lesions and noncavitated and cavitated root lesions were available, we were not able to identify published RCTs providing data about the effect of SDF on noncavitated lesions on approximal surfaces. The panel was eager to explore this indication for SDF because of the very low certainty in the evidence informing the use of other interventions on approximal surfaces. We identified the protocol of an ongoing RCT that may include data about this indication.[69] At the time of publication, we were not able to summarize these data or provide a recommendation for the use of SDF on noncavitated lesions on approximal surfaces.

Finally, we would have benefited from having a minimum set of patient-important outcomes for optimal decision making. This set should be developed and defined with the purpose of achieving standardization in the way outcomes are measured, reported, and summarized in RCTs and systematic reviews.

CONCLUSIONS

To arrest or reverse noncavitated carious lesions in both primary and permanent teeth, the expert panel suggests clinicians prioritize the use of sealants plus 5% NaF varnish on occlusal surfaces, 5% NaF varnish on approximal surfaces, and 1.23% APF gel or 5% NaF varnish alone on facial or lingual surfaces. The expert panel also suggests clinicians prioritize the use of 5,000 ppm fluoride (1.1% NaF) toothpaste or gel to arrest or reverse noncavitated and cavitated lesions on root surfaces of permanent teeth. To arrest advanced cavitated carious lesions on coronal surfaces of primary teeth, the expert panel recommends clinicians prioritize the use of 38% SDF solution biannually. The expert panel extrapolated these results to suggest that clinicians could use 38% SDF solution biannually to arrest advanced cavitated lesions on coronal surfaces of permanent teeth as well. The biannual application of 38% solution SDF for advanced cavitated lesions may be relevant if access to care is limited, for uncooperative patients, or for patients when general anesthetic is not considered safe. ■

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2018.07.002.

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APPENDIX

METHODS

Panel configuration and conflicts of interest

The American Dental Association (ADA) Council on Scientific Affairs convened and approved an expert panel. Panel nominees filled out financial and intellectual conflicts of interest forms, and the methodologists subsequently reviewed them. We excluded nominees with major conflicts from the panel. We made these forms available to the panel at the beginning of all in-person meetings (December 2016, October 2017, and February 2018) and updated them periodically. We asked panel members who were highly conflicted to refrain from participating in the discussions when we were formulating recommendations pertaining to their conflict.

Outcomes

The panel defined outcomes important for decision making. These included arrest or reversal of noncavitated and cavitated carious lesions, nausea, fluorosis, vomiting, allergic reactions, staining, tooth sensitivity, soft-tissue trauma, progression of symptoms, pulpal health, lack of retention (for sealants), premature loss or extraction, and secondary caries.

Retrieving evidence

The recommendations contained in this guideline are informed by the results of a systematic review (O. Urquhart, MPH, unpublished data, June 2018). A health sciences librarian (L.B.) searched MEDLINE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Embase to identify relevant articles for the review. Two of us (O.U., M.P.T.) screened all identified references in duplicate at the title and abstract levels and then during a second stage at a full-text level. Four of us (M.P.T., O.U., L.P., an author of the related systematic review) then extracted data from the included studies and appropriately synthesized the data by using a network meta-analysis. A full report of methods and results from this guideline can be found in our accompanying systematic review (O. Urquhart, MPH, unpublished data, June 2018).

Relative and absolute treatment effects

We calculated relative risks and 95% CIs for dichotomous data and mean differences and 95% CIs for continuous data. The numbers presented in the text are the rounded versions of the numbers presented in the tables. In some cases, we could not pool data in the network meta-analysis. We still included these data, considered unpooled, and we reported relative risks and mean differences at a study level or as the study authors described. We displayed all data from the network meta-analysis by using a modified version of the summary-of-findings tables for the network meta-analysis (J.J. Yepes-Nuñez, MD, MSc, written communication, March 2018). We also calculated absolute treatment effects by using 3 illustrative baseline probabilities for arrest or reversal of carious lesions (20%, 50%, and 70%). For example, someone in the 70% category has a 70% baseline probability for arrest or reversal of their carious lesions without any intervention. The panel chose these numbers arbitrarily to represent different risk profiles that clinicians may see in practice.

Certainty in the evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for the network meta-analysis to assess the certainty in the evidence (high, moderate, low, or very low) at an outcome level for each of the comparisons.[e1] We assessed the domains of risk of bias, inconsistency, imprecision, publication bias, and indirectness for all direct comparisons according to guidance from the GRADE working group.[16] We further considered intransitivity when assessing the certainty of indirect estimates. Finally, when assessing the certainty in the evidence of the network estimates, we considered local incoherence between the direct and indirect estimates. When we could not include studies in the network meta-analysis, we assessed the certainty in the evidence at a study level.

Stakeholder and public feedback

Throughout the guideline development process, we engaged both internal ADA stakeholders and external stakeholder organizations. Internal stakeholders were the Council on Advocacy for Access and Prevention, Council on Dental Benefit Programs, and Council on Dental Practice. External stakeholders were the Academy of Dental Materials, Academy of General Dentistry, Academy of Operative Dentistry, American Academy of Pediatric Dentistry, American Association of Endodontists, American Association of Public Health Dentistry, American Dental Hygienists' Association, Association of State and Territorial Dental Directors, National Institute of Dental and Craniofacial Research and Oral Health America.

We contacted stakeholders twice throughout the process; first to provide feedback regarding the scope, purpose, target audience, and clinical questions for the guideline and a second time to review the recommendation statements. In addition, we posted the recommendation statements on the ADA Center for Evidence-Based Dentistry's Web site (ebd.ada.org) to offer the general public an opportunity to provide feedback. We considered all feedback and included it in the manuscript whenever appropriate.

Updating process

The ADA Center for Evidence-Based Dentistry updates its guidelines every 5 years or whenever newly published evidence could result in a change in the direction or strength of recommendations. We use digital platforms such as MAGICapp and RevMan to store all of our data, thereby facilitating an efficient updating process. Updates and chairside resources for clinicians are available at the ADA Center for Evidence-Based Dentistry Web site.

RESULTS

Noncavitated lesions on occlusal surfaces

After 8 to 12 months of follow-up, for a population with a 50% chance of arresting or reversing noncavitated carious lesions on occlusal surfaces, 19 more to 118 more carious lesions would be arrested or reversed of 100 lesions treated with sealants plus 5% sodium fluoride (NaF) varnish, sealants alone, 5% NaF varnish alone, 1.23% acidulated phosphate fluoride gel, 5% NaF varnish, resin infiltration and 5% NaF varnish, or 0.2% NaF mouthrinse plus supervised toothbrushing compared with no treatment.

Noncavitated lesions on approximal surfaces

After 12 through 30 months of follow-up, for a population with a 50% chance of arresting or reversing noncavitated carious lesions on approximal surfaces, 56 more to 178 more carious lesions would be arrested or reversed of 100 lesions treated with a combination of resin infiltration and 5% NaF varnish, resin infiltration alone, or sealants alone compared with no treatment.

Noncavitated lesions on facial or lingual surfaces

After 12 through 30 months of follow-up, for a population with a 50% chance of arresting or reversing noncavitated carious lesions on facial or lingual surfaces, 12 more to 74 more carious lesions would be arrested or reversed of 100 lesions treated with 5% NaF varnish, 1.23% acidulated phosphate fluoride gel, or 10% casein phosphopeptide—amorphous calcium phosphate paste compared with no treatment, oral health education, and a placebo cream, respectively.

Noncavitated lesions on any coronal tooth surfaces

After 12 through 30 months of follow-up, for a population with a 50% chance of arresting or reversing noncavitated carious lesions on any coronal tooth surface, 2 more to 63 more carious lesions would be arrested or reversed of 100 lesions treated with 5% NaF varnish, 1.23% acidulated phosphate fluoride gel, or 10% casein phosphopeptide—amorphous calcium phosphate paste compared with no treatment.

Noncavitated and cavitated lesions on root surfaces

After 3 through 12 months of follow-up, for a population with a 50% chance of arresting or reversing noncavitated and cavitated carious lesions on root surfaces, 34 more to 98 more carious lesions would be arrested or reversed of 100 lesions treated with 5,000 parts per million fluoride (1.1% NaF) toothpaste or gel, a combination of 1% chlorhexidine and thymol varnish, 38% silver diamine fluoride solution, a combination of 38% silver diamine fluoride solution and potassium iodide, or 5% NaF varnish compared with no treatment.

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eTable 1. Summary of findings: nonrestorative treatments for the arrest of advanced cavitated lesions on any coronal tooth surface.

TOTAL NO. OF UNPOOLED STUDIES: 4 RANDOMIZED CONTROLLED TRIALS*,†,‡,§	NO. OF PEOPLE AT FOLLOW-UP/ NO. OF LESIONS AT LONGEST FOLLOW-UP	SURFACE	STUDY ARM: DOSE, DURATION, OR FREQUENCY	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE¶
					Without Intervention (%)#	With Intervention	Difference	
Duangthip and Colleagues[20] and Duangthip and Colleagues[19]	309/1,877	Any surface (occlusal, approximal, facial or lingual)	30% SDF** solution annually versus 30% SDF solution once per week for 3 weeks		70 per 100	102 per 100	32 per 100 more	High
							(From 15 more to 52 more)	
				1.45	50 per 100	73 per 100	23 per 100 more	
				(1.21 to 1.73)			(From 11 more to 37 more)	
					20 per 100	29 per 100	9 per 100 more	
							(From 4 more to 15 more)	
			30% SDF solution annually versus 5% NaF†† varnish once per week for 3 weeks		70 per 100	99 per 100	29 per 100 more	High
				1.41			(From 14 more to 46 more)	
					50 per 100	71 per 100	21 per 100 more	
				(1.20 to 1.66)			(From 10 more to 33 more)	
					20 per 100	28 per 100	8 per 100 more	
							(From 4 more to 13 more)	
			30% SDF solution once per week for 3 weeks versus 5% NaF varnish once per week for 3 weeks		70 per 100	68 per 100	2 per 100 fewer	Moderate (imprecision‡‡)
							(From 14 fewer to 13 more)	

* Sources: Duangthip and colleagues[20] and Duangthip and colleagues[19] (30-month follow-up, primary dentition): black staining was reported as an adverse event. † Sources: Fung and colleagues,[21] Duangthip and colleagues[18] and Fung and colleagues[22] (30-month follow-up, primary dentition): lesions treated with 38% SDF had a statistically significantly increased chance of becoming black than those receiving 12% SDF. Lesions treated semiannually also had a higher chance of becoming black than those treated annually. There was no significant difference in tooth pain, gingiva pain, gingiva swelling, or gingiva bleaching among the 4 groups; these adverse events affected a small proportion of children in each group (1%-7%). ‡ Source: Yee and colleagues[17] (24-month follow-up, primary dentition): The authors reported results as mean differences (MD): −38% SDF and breakfast tea versus no treatment: MD, 1.20; 95% confidence interval [CI], 0.49 to 1.91; 12% SDF versus no treatment: MD, 0.50; 95% CI, −0.21 to 1.21; 38% SDF versus no treatment: MD, 1.10; 95% CI, 0.39 to 1.81; 38% SDF versus 12% SDF: MD, 0.60; 95% CI, −0.23 to 1.43; 38% SDF versus 38% SDF and tea: MD, −0.10; 95% CI, −0.93 to 0.73; 12% SDF versus 38% SDF and tea: MD, −0.70; 95% CI, −1.53 to 0.13. The authors also reported results for 6 and 12 months. § Source: Llodra and colleagues[23] (36 months, primary dentition): after 36 months of follow-up, on average, the 38% SDF group had 0.3 surfaces with arrested caries, whereas the control group had 0.1 ($P < .05$). The SDF group had a higher percentage of black stains (97%) than did the control group, in which only 48% of the inactive lesions were black ($P < .001$). Compared with the control participants, the children treated with SDF had a higher proportion of black stains in inactive lesions ($P < .001$). ¶ When these data were used to inform recommendation 6, the certainty in the evidence was downgraded because of serious issues of indirectness. There is no direct evidence available informing the effectiveness of any concentration of SDF in permanent teeth. # The percentages (20%, 50%, 70%) indicate illustrative baseline probabilities for the arrest or reversal of carious lesions. ** SDF: Silver diamine fluoride. †† NaF: Sodium fluoride. ‡‡ Serious issues of imprecision; 95% CI suggests a moderate harm and moderate benefit. §§ Serious issues of imprecision; 95% CI suggests a small benefit and a moderate benefit.

eTable 1. Continued

TOTAL NO. OF UNPOOLED STUDIES: 4 RANDOMIZED CONTROLLED TRIALS*,†,‡,§	NO. OF PEOPLE AT FOLLOW-UP/ NO. OF LESIONS AT LONGEST FOLLOW-UP	SURFACE	STUDY ARM: DOSE, DURATION, OR FREQUENCY	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE¶
					Without Intervention (%)#	With Intervention	Difference	
				0.97	50 per 100	49 per 100	2 per 100 fewer	
				(0.80 to 1.18)			(From 10 fewer to 9 more)	
					20 per 100	19 per 100	−1 per 100 fewer	
							(From 4 fewer to 4 more)	
Fung and Colleagues,[21] Duangthip and Colleagues,[18] and Fung and Colleagues[22]	799/3,790	Any surface (mesial, occlusal, approximal, distal, facial or lingual)	12% SDF solution annually versus 12% SDF biannually		70 per 100	66 per 100	4 per 100 fewer	High
							(From 9 fewer to 1 more)	
				0.94	50 per 100	47 per 100	3 per 100 fewer	
				(0.87 to 1.02)			(From 7 fewer to 1 more)	
					20 per 100	19 per 100	1 per 100 fewer	
							(From 3 fewer to 0 fewer)	
			38% SDF solution annually versus 12% SDF solution annually		70 per 100	85 per 100	15 per 100 more	High
							(From 9 more to 21 more)	
				1.21	50 per 100	61 per 100	11 per 100 more	
				(1.13 to 1.3)			(From 7 more to 15 more)	
					20 per 100	24 per 100	4 per 100 more	
							(From 3 more to 6 more)	
			38% SDF solution biannually versus 12% SDF solution biannually		70 per 100	90 per 100	20 per 100 more	High
							(From 15 more to 27 more)	
				1.29	50 per 100	65 per 100	15 per 100 more	

eTable 1. Continued

TOTAL NO. OF UNPOOLED STUDIES: 4 RANDOMIZED CONTROLLED TRIALS*,†,‡,§	NO. OF PEOPLE AT FOLLOW-UP/ NO. OF LESIONS AT LONGEST FOLLOW-UP	SURFACE	STUDY ARM: DOSE, DURATION, OR FREQUENCY	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE¶
					Without Intervention (%)#	With Intervention	Difference	
				(1.21 to 1.38)			(From 11 more to 19 more)	
					20 per 100	26 per 100	6 per 100 more	
							(From 4 more to 8 more)	
			38% SDF solution biannually versus 38% SDF solution annually		70 per 100	79 per 100	9 per 100 more	Moderate (imprecision§§)
							(From 5 more to 14 more)	
				1.13	50 per 100	57 per 100	7 per 100 more	
				(1.07 to 1.2)			(From 4 more to 10 more)	
					20 per 100	23 per 100	3 per 100 more	
							(From 1 more to 4 more)	

eTable 2. Summary of findings: additional follow-up times for nonrestorative treatments for the arrest of advanced cavitated lesions on any coronal tooth surface.

TOTAL NO. OF UNPOOLED STUDIES: 4*,†,‡,§ (7 REPORTS)	STUDY ARM (DOSE, DURATION, OR FREQUENCY)	RELATIVE RISK (95% CONFIDENCE INTERVAL) AND CERTAINTY IN THE EVIDENCE			
Duangthip and Colleagues[20] and Duangthip and Colleagues[19]	30% SDF¶ solution (annually) 30% SDF (once per week for 3 weeks, not reapplied annually) 5% NaF varnish (once per week for 3 weeks, not reapplied annually)	30% SDF solution annually versus 30% SDF once per week for 3 weeks 30 months: 1.45 (1.21 to 1.73); certainty: high 18 months: 1.13 (0.95 to 1.34); certainty: moderate (serious issues of imprecision**) 12 months: 0.72 (0.56 to 0.91); certainty: moderate (serious issues of imprecision**)	30% SDF solution annually versus 5% NaF# varnish once per week for 3 weeks 30 months: 1.41 (1.20 to 1.66); certainty: high 18 months: 1.47 (1.22 to 1.76); certainty: high 12 months: 1.48 (1.11 to 1.97); certainty: high	30% SDF solution once per week for 3 weeks versus 5% NaF varnish once per week for 3 weeks 30 months: 0.97 (0.80 to 1.18); certainty: moderate (serious issues of imprecision**) 18 months: 1.30 (1.07 to 1.57); certainty: high 12 months: 2.08 (1.59 to 2.71); certainty: high	Not applicable
Fung and Colleagues,[21] Duangthip and Colleagues[18] and Fung and Colleagues[22]	12% SDF solution (annually) 12% SDF solution (biannually) 38% SDF solution (annually) 38% SDF solution (biannually)	12% SDF solution annually versus 12% SDF solution biannually 30 months: 0.94 (0.87 to 1.02); certainty: high 24 months: 0.91 (0.84 to 0.98); certainty: moderate (serious issues of imprecision**) 18 months: 0.91 (0.83 to 0.99); certainty: moderate (serious issues of imprecision**) 12 months: 0.85 (0.77 to 0.93); certainty: moderate (serious issues of imprecision**)	38% SDF solution biannually versus 38% solution SDF annually 30 months: 1.13 (1.07 to 1.20); certainty: moderate (serious issues of imprecision**) 24 months: 1.20 (1.13 to 1.27); certainty: high 18 months: 1.15 (1.09 to 1.23); certainty: moderate (serious issues of imprecision**) 12 months: 1.21 (1.12 to 1.30); certainty: high	38% SDF solution biannually versus 12% SDF solution biannually 30 months: 1.29 (1.21 to 1.38); certainty: high 24 months: 1.29 (1.21 to 1.38); certainty: high 18 months: 1.34 (1.25 to 1.43); certainty: high 12 months: 1.30 (1.21 to 1.41); certainty: high	38% SDF solution annually versus 12% SDF solution annually 30 months: 1.21 (1.13 to 1.30); certainty: high 24 months: 1.19 (1.10 to 1.28); certainty: high 18 months: 1.27 (1.18 to 1.38); certainty: high 12 months: 1.27 (1.16 to 1.40); certainty: high

* Sources: Duangthip and colleagues[20] and Duangthip and colleagues[19] (primary dentition): black staining was reported as an adverse event. † Sources: Fung and colleagues[21] and Duangthip and colleagues[18] and Fung and colleagues[22] (primary dentition): lesions treated with 38% SDF had a statistically significantly increased chance of becoming black compared with those receiving 12% SDF. Lesions treated semiannually also had a higher chance of becoming black than did those treated annually. There was no significant difference in tooth pain, gingiva pain, gingiva swelling, or gingiva bleaching among the 4 groups; these adverse events affected a small proportion of children in each group (1%-7%). ‡ Source: Yee and colleagues[17] (24-month follow-up, primary dentition): the authors reported results as mean differences (MD): −38% SDF and tea versus no treatment: MD, 1.20, 95% confidence interval [CI], 0.49 to 1.91; 12% SDF versus no treatment: MD, 0.50, 95% CI, −0.21 to 1.21; 38% SDF versus no treatment: MD, 1.10, 95% CI, 0.39 to 1.81; 38% SDF versus 12% SDF: MD, 0.60, 95% CI, −0.23 to 1.43; 38% SDF versus 38% SDF and tea: MD, −0.10; 95% CI, −0.93 to 0.73; 12% SDF versus 38% SDF and tea: MD, −0.70; 95% CI, −1.53 to 0.13. The authors also reported results for 6 and 12 months. § Source: Llodra and colleagues[23] (36 months, primary dentition): after 36 months of follow-up, on average, the 38% SDF group had 0.3 surfaces with arrested caries, whereas the control group had 0.1 ($P < .05$). The SDF group had a higher percentage of black stains (97%) than did the control group, in which only 48% of the inactive lesions were black ($P < .001$). Compared with the control participants, the children treated with SDF had a higher proportion of black stains in inactive lesions ($P < .001$). ¶ SDF: Silver diamine fluoride. # NaF: Sodium fluoride. ** Serious issues of imprecision.

eTable 3. Summary of findings: nonrestorative treatments for the arrest or reversal of noncavitated lesions on occlusal surfaces.

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 7[*,†,‡,§,¶,#,**] TOTAL NO. OF PARTICIPANTS IN NETWORK: 694[††] TOTAL NO. OF UNPOOLED STUDIES: 1 RANDOMIZED CONTROLLED TRIAL[‡‡]	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE	P-SCORE (RANKING)[§§]	INTERPRETATION OF FINDINGS
		Without Intervention (%)[¶¶]	**With Intervention**	**Difference**			
0.2% NaF[##] Mouthrinse plus Supervised Toothbrushing[*]		70 per 100	137 per 100	67 per 100 more	Moderate (risk of bias[***])	0.35 (6/7)	Superior
(Indirect Evidence)				(From 38 more to 102 more)			
	1.95	50 per 100	98 per 100	48 per 100 more			
	(1.54 to 2.46)			(From 27 more to 73 more)			
		20 per 100	39 per 100	19 per 100 more			
				(From 11 more to 29 more)			
1.23% Acidulated Phosphate Fluoride Gel[†] (Direct Evidence)		70 per 100	149 per 100	79 per 100 more	Moderate (risk of bias[†††])	0.53 (3/7)	Superior
				(From 55 more to 108 more)			
	2.13	50 per 100	107 per 100	57 per 100 more			
	(1.79 to 2.54)			(From 40 more to 77 more)			
		20 per 100	43 per 100	23 per 100 more			
				(From 16 more to 31 more)			

* Source: Florio and colleagues[31] (12-month follow-up, permanent dentition): the use of a resin-modified glass ionomer sealant resulted in a 65.5% (19/29) retention rate at 12-month follow-up. † Source: Agrawal and Pushpanjali[26] (12-month follow-up, mixed dentition). ‡ Source: Autio-Gold and Courts[33] (9-month follow-up, primary dentition). § Source: Bakhshandeh and Ekstrand[27] (8- to 34-month follow-up; mean, 22 months; primary dentition): 5% NaF varnish and resin-based sealant. ¶ Source: Honkala and colleagues[32] (12-month follow-up, primary dentition): of the 345 resin-sealed occlusal surfaces, 73.0% (252) were retained fully after 1-year follow-up, whereas 15.1% (52) experienced partial retention. # Source: da Silveira and colleagues[30] (12-month follow-up, permanent dentition): throughout the 12-month study, 40.74% (11/27) of teeth in the glass ionomer sealant group had total retention of the sealant, 40.74% (11/27) had 1 sealant replacement, and 18.52% (5/27) had 2 sealant replacements. ** Source: Borges and colleagues[29] (12-month follow-up, mixed dentition): in the resin-sealant group, 88.5% (23/26) of teeth had full retention, 7.7% (2/26) had partial retention, and 3.85% (1/26) had total loss of sealant at a 12-month follow-up. †† Source: Florio and colleagues[31] did not report loss to follow-up at a person level. They reported the total number of participants randomly assigned to each group at baseline; Borges and colleagues[29] and da Silveira and colleagues[30] did not report loss to follow-up at a person level or the total number of participants randomly assigned to each group at baseline. The number reported is the total number of participants at baseline. The guideline authors used data from occlusal surfaces only from Agrawal and Pushpanjali[26] and Autio-Gold and Courts[33] Although the study authors reported the number of lesions on occlusal surfaces, they did not report the number of participants who had lesions on occlusal surfaces. The number reported is the total number of participants at follow-up; investigators in other studies included in the network reported the total number of participants at follow-up. ‡‡ Source: Altenburger and colleagues[27] (3-week follow-up, permanent dentition): the use of 10% casein phosphopeptide−amorphous calcium phosphate daily for 3 weeks resulted in a 400% increase in caries arrestment (relative risk, 5.00; 95% confidence interval, 0.25 to 98.97) compared with 1,450 parts per million toothpaste daily at 3 weeks of follow-up. §§ The lower the value, the higher the position in the ranking. ¶¶ The percentages (20%, 50%, 70%) indicate illustrative baseline probabilities for the arrest or reversal of carious lesions. ## NaF: Sodium fluoride. *** Serious issues of risk of bias exist because of unclear randomization technique and no information or inadequate allocation concealment. Also, it is unclear whether the outcome assessor, personnel, or patients were blinded and whether outcome data were complete. ††† Serious issues of risk of bias exist because of unclear methods related to allocation concealment, and blinding of participants and personnel. ‡‡‡ Serious issues of risk of bias exist because of unclear methods related to random sequence generation, allocation concealment, and blinding of personnel and participants. §§§ Serious issues of risk of bias exist because of unclear methods related to blinding of personnel or participants, allocation concealment, blinding of outcome assessors, and random sequence generation. ¶¶¶ Serious issues of risk of bias exist because of inadequate allocation concealment and incomplete outcome data. Also, methods related to random assignment or blinding of participants and personnel are unclear. ### The studies informing the no-treatment group consist of no treatment and oral health education.[26,29,30,32,33]

eTable 3. Continued

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 7[*,†,‡,§,¶,#,**] TOTAL NO. OF PARTICIPANTS IN NETWORK: 694[††] TOTAL NO. OF UNPOOLED STUDIES: 1 RANDOMIZED CONTROLLED TRIAL[‡‡]	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE	P-SCORE (RANKING)[§§]	INTERPRETATION OF FINDINGS
		Without Intervention (%)[¶¶]	With Intervention	Difference			
5% NaF Varnish[*,‡,§,¶] (Direct and Indirect Evidence)		70 per 100	138 per 100	68 per 100 more	Moderate (risk of bias[‡‡‡])	0.39 (5/7)	Superior
				(From 44 more to 98 more)			
	1.97	50 per 100	99 per 100	49 per 100 more			
	(1.63 to 2.40)			(From 32 more to 70 more)			
		20 per 100	39 per 100	19 per 100 more			
				(From 13 more to 28 more)			
Resin Infiltration plus 5% NaF Varnish[§] (Indirect Evidence)		70 per 100	224 per 100	154 per 100 more	Moderate (risk of bias[§§§])	0.89 (2/7)	Superior
				(From 87 more to 249 more)			
	3.20	50 per 100	160 per 100	110 per 100 more			
	(2.24 to 4.56)			(From 62 more to 178 more)			
		20 per 100	64 per 100	44 per 100 more			
				(From 25 more to 71 more)			
Sealant plus 5% NaF Varnish[§,¶] (Indirect Evidence)		70 per 100	235 per 100	165 per 100 more	Moderate (risk of bias[§§§])	0.94 (1/7)	Superior
				(From 99 more to 255 more)			
	3.35	50 per 100	168 per 100	118 per 100 more			
	(2.42 to 4.64)			(From 71 more to 182 more)			
		20 per 100	67 per 100	47 per 100 more			
				(From 28 more to 73 more)			

eTable 3. Continued

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 7[*,†,‡,§,¶,#,**] TOTAL NO. OF PARTICIPANTS IN NETWORK: 694[††] TOTAL NO. OF UNPOOLED STUDIES: 1 RANDOMIZED CONTROLLED TRIAL[‡‡]	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE	P-SCORE (RANKING)[§§]	INTERPRETATION OF FINDINGS
		Without Intervention (%)[¶¶]	With Intervention	Difference			
Sealant[*,#,] (Direct and Indirect Evidence)**		70 per 100	139 per 100	69 per 100 more	Moderate (risk of bias[¶¶¶])	0.40 (4/7)	Superior
				(From 43 more to 101 more)			
	1.98	50 per 100	99 per 100	49 per 100 more			
	(1.62 to 2.44)			(From 31 more to 72 more)			
		20 per 100	40 per 100	20 per 100 more			
				(From 12 more to 29 more)			
No Treatment[†, ‡,¶, #,,###]**					Reference comparator	0.00 (7/7)	Reference comparator
	Reference comparator	Not estimable	Not estimable	Reference comparator			

eTable 4. Summary of findings: nonrestorative treatments for the arrest or reversal noncavitated lesions on approximal surfaces.

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 6 RANDOMIZED CONTROLLED TRIALS[*,†,‡,§,¶,#] TOTAL NO. OF PARTICIPANTS IN NETWORK: 232 TOTAL NO. OF UNPOOLED STUDIES: 7 RANDOMIZED CONTROLLED TRIALS[**,††,‡‡,§§,¶¶,##,***]	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE	P-SCORE (RANKING)[†††]	INTERPRETATION OF FINDINGS
		Without Intervention (%)[‡‡‡]	With Intervention	Difference			
5% NaF[§§§] Varnish[*,†] (Indirect Evidence)		70 per 100	160 per 100	90 per 100 more	Very low (risk of bias[¶¶¶] and imprecision[###])	0.51 (3/5)	May be superior
				(From 18 fewer to 427 more)			
	2.29	50 per 100	114 per 100	65 per 100 more			
	(0.74 to 7.10)			(From 13 fewer to 305 more)			
		20 per 100	46 per 100	26 per 100 more			
				(From 5 fewer to 122 more)			
Resin Infiltration[‡,§] (Direct and Indirect Evidence)		70 per 100	148 per 100	78 per 100 more	Low (risk of bias[****] and imprecision[††††])	0.49 (4/5)	May be superior
				(From 6 more to 219 more)			

* Source: Ekstrand and colleagues[42] (12-month follow-up, primary dentition). † Source: Gomez and colleagues[43] (24-month follow-up, mixed dentition). ‡ Source: Martignon and colleagues[45] (12-month follow-up, permanent dentition). § Sources: Meyer-Lueckel and colleagues[47] and Paris and colleagues[48] (36-month follow-up, permanent dentition). Additional follow-ups: 18 months: resin infiltration versus no treatment: relative risk [RR], 1.47; 95% confidence interval [CI], 1.08 to 2.00. ¶ Source: Martignon and colleagues[46] (30-month follow-up, primary dentition): 73.6% of participants experienced light pain during elastic band placement and 65.8% experienced light pain during the sealing process. # Source: Martignon and colleagues[44] (18-month follow-up, permanent dentition). ** Source: Meyer-Lueckel and colleagues[35] (18-month follow-up, mixed dentition): additional fluoride varnish was applied at the discretion of each dentist during the 6-month recall. Therefore, the guideline authors removed this study from the network because they could not account for background fluoride varnish. However, in the resin infiltration group, 94.6% (176/186) of participants experienced no progression compared with 68.8% (128/186) participants in the mock treatment group (RR, 1.38; 95% CI, 1.24 to 1.52). †† Source: Moberg Sköld and colleagues[36] (36-month follow-up, permanent dentition): in patients receiving 0.2% NaF mouthrinse 12 times per year, 59% of caries that could have progressed were prevented compared with findings in patients receiving 6 mouthrinses per year (PF = 30%), 27 mouthrinses per year (PF = 47%), and 20 mouthrinses per year (preventive fraction = 41%). ‡‡ Source: Moberg Sköld and colleagues[37] (36-month follow-up, permanent dentition): the use of 5% NaF varnish twice per year at 6-month intervals resulted in a 17% increase in the chance of experiencing caries arrestment (RR, 1.17; 95% CI, 1.07 to 1.27), the use of 5% NaF varnish 3 times per year all in 1 week, resulted in a 13% increase in the chance of experiencing caries arrestment (RR, 1.13; 95% CI, 1.03 to 1.24), and the use of 5% NaF varnish 8 times per year with 1-month intervals resulted in a 15% increase in the chance of experiencing caries arrestment (RR, 1.15; 95% CI, 1.06 to 1.26) compared with results with no additional fluoride varnish. All the groups in this study received 5% NaF varnish regularly as part of a school program. §§ Source: Modéer and colleagues[38] (36-month follow-up, permanent dentition): the use of 5% NaF varnish (every third month for 3 years) and 0.2% NaF mouthrinse (every 14 days) resulted in a 4% decrease in caries arrestment (RR, 0.96; 95% CI, 0.51 to 1.80) compared with results with 0.2% NaF mouthrinse (every 14 days) at 3 years of follow-up. ¶¶ Source: Petersson and colleagues[39] (36-month follow-up, mixed dentition): patients receiving 5% NaF varnish 3 times per week once per year for 3 years reported 116 surfaces arrested and reversed compared with 78 surfaces arrested and reversed in those receiving 5% NaF varnish every 6 months for 3 years (no total number of surfaces per group reported). ## Source: Peyron and colleagues[40] (12- and 24-month follow-ups, primary dentition): after 1 year of follow-up, of 41 people in the 5% NaF varnish arm, 48.8% (n = 20) of the enrolled patients with 1 or more superficial enamel carious lesions experienced no progression of carious lesions compared with 17.2% (n = 5) of the 29 people with who did not receive 5% NaF varnish. After 2 years of follow-up, of 42 people with 1 or more superficial enamel carious lesions receiving 5% NaF varnish, 33.3% (n = 14) did not experience progression of carious lesions compared with 8.8% (n = 3) of the 34 who did not receive 5% NaF varnish. *** Source: Trairatvorakul and colleagues[41] (12-month follow-up, permanent dentition): The use of sealants and 1.23% acidulated phosphate fluoride gel (at baseline and 6-month recall) resulted in a 1,950% increase in caries arrestment (RR, 20.05; 95% CI, 5.31 to 79.21) compared with 1.23% acidulated phosphate fluoride gel (at baseline and 6-month recall) after 1 year of follow-up. ††† The lower the value, the higher the position in the ranking. ‡‡‡ The percentages (20%, 50%, 70%) indicate illustrative baseline probabilities for the arrest or reversal of carious lesions. §§§ NaF: Sodium fluoride. ¶¶¶ Serious issues of risk of bias exist because of no information regarding allocation concealment or blinding of participants or personnel and incomplete outcome data. ### Serious issues of imprecision; 95% CI suggests large harm and large benefit. **** Serious issues of risk of bias exist because of no information about blinding of participants or personnel and unclear allocation concealment. †††† Serious issues of imprecision; 95% CI suggests a small benefit or a large benefit. ‡‡‡‡ Serious issues of risk of bias due to unclear allocation concealment, incomplete outcome assessment, and no information about blinding of participants and clinicians; in other cases, clinicians were not blinded at all. §§§§ Serious issues of imprecision; 95% CI suggests no benefit or a very large benefit. ¶¶¶¶ Serious inconsistency (I^2 = 87%; P = .0004). #### Studies informing the no-treatment group consist of placebo sealing and flossing instructions, flossing and 1,000 to 1,500 parts per million dentifrice, and mock treatment using water.[44-46,48]

eTable 4. Continued

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 6 RANDOMIZED CONTROLLED TRIALS[*,†,‡,§,¶,#] TOTAL NO. OF PARTICIPANTS IN NETWORK: 232 TOTAL NO. OF UNPOOLED STUDIES: 7 RANDOMIZED CONTROLLED TRIALS[**,††,‡‡,§§,¶¶,##,***]	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE	P-SCORE (RANKING)[†††]	INTERPRETATION OF FINDINGS
		Without Intervention (%)[‡‡‡]	With Intervention	Difference			
	2.11	50 per 100	106 per 100	56 per 100 more			
	(1.08 to 4.13)			(From 4 more to 157 more)			
		20 per 100	42 per 100	22 per 100 more			
				(From 2 more to 63 more)			
Resin Infiltration plus 5% NaF Varnish[*] (Indirect Evidence)		70 per 100	321 per 100	251.3 per 100 more	Very low (risk of bias[‡‡‡‡] and imprecision[§§§§])	0.89 (1/5)	May be superior
				(From 0 fewer to 1,392 more)			
	4.59	50 per 100	230 per 100	180 per 100 more			
	(1.00 to 20.88)			(From 0 fewer to 994 more)			
		20 per 100	92 per 100	72 per 100 more			
				(From 0 fewer to 398 more)			
Sealant[†,‡,¶,#] (Direct and Indirect Evidence)		70 per 100	169 per 100	99 per 100 more	Low (risk of bias[¶¶¶] and inconsistency[¶¶¶¶])	0.59 (2/5)	May be superior
				(From 18 more to 251 more)			
	2.41	50 per 100	121 per 100	71 per 100 more			
	(1.26 to 4.58)			(From 13 more to 179 more)			
		20 per 100	48 per 100	28 per 100 more			
				(From 5 more to 72 more)			
No Treatment[‡,§,¶,#,####]							
	Reference comparator	Not estimable	Not estimable	Reference comparator	Reference comparator	0.03 (5/5)	Reference comparator

eTable 5. Summary of findings: nonrestorative treatments for noncavitated lesions on facial or lingual surfaces.

TOTAL NO. OF UNPOOLED STUDIES: 5 RANDOMIZED CONTROLLED TRIALS*,†,‡,§,¶	NO. OF PEOPLE AT FOLLOW-UP/ NO. OF LESIONS AT LONGEST FOLLOW-UP	STUDY ARM (DOSE, DURATION, OR FREQUENCY)	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE
				Without Intervention (%)#	With Intervention	Difference	
Agrawal and Pushpanjali[26]	257‡‡/374	1.23% acidulated phosphate fluoride gel (2 applications) and oral health education		70 per 100	173 per 100	103 per 100 more	Moderate (risk of bias¶¶)
						(From 67 more to 149 more)	
			2.47	50 per 100	124 per 100	74 per 100 more	
			(1.95 to 3.13)			(From 48 more to 107 more)	
				20 per 100	49 per 100	29 per 100 more	
						(From 19 more to 43 more)	
		Oral health education					Reference comparator
			Reference comparator	Not estimable	Not estimable	Reference comparator	
Autio-Gold and Courts[33]	124‡‡/150	5% NaF varnish (2 applications)		70 per 100	161 per 100	91 per 100 more	Low (risk of bias§§)
						(From 41 more to 164 more)	
			2.30	50 per 100	115 per 100	65 per 100 more	
			(1.58 to 3.34)			(From 29 more to 117 more)	
				20 per 100	46 per 100	26 per 100 more	
						(From 12 more to 47 more)	
		No treatment					Reference comparator
			Reference comparator	Not estimable	Not estimable	Reference comparator	

* Source: Agrawal and Pushpanjali[26] (12-month follow-up, mixed dentition): data for 12 and 18 months are presented in the Appendix (available online at the end of this article). † Source: Autio-Gold and Courts[33] (9-month follow-up, primary dentition). ‡ Source: Bailey and colleagues[52] (12-week follow-up, mixed dentition): data for 4- and 8-week follow-up are presented in the Appendix (available online at the end of this article). One or more adverse events were reported for 86% of participants (n = 39) but no information on the nature of them. There was also 1 or more reported gastrointestinal symptoms in the casein phosphopeptide−amorphous calcium phosphate cream arm. § Source: Turska-Szybka and colleagues[51] (12-month follow-up, primary dentition): the guideline authors could not calculate a relative risk or mean difference. Of the 41 children treated with resin infiltration and 5% NaF fluoride varnish, 75.6% (n = 31) showed no progression or continued activity of the treated spots at any examination. Of the 40 children treated with 5% NaF fluoride varnish, 32.5% (n = 13) of white-spot lesions showed no progression or continued activity (total number of lesions not reported). ¶ Source: Bonow and colleagues[50] (8-week follow-up, mixed dentition): the guideline authors could not calculate a relative risk or mean difference. Patients receiving 1.23% acidulated phosphate fluoride gel had a 65% increased probability for arresting or reversing in the facial or lingual surfaces compared with those in the placebo arm after 8 weeks of follow-up (adjusted relative risk, 1.65; 95% confidence interval, 0.69 to 3.96). # The percentages (20%, 50%, 70%) indicate illustrative baseline probabilities for the arrest or reversal of carious lesions. ** NaF: Sodium fluoride. †† Serious issues of risk of bias exist because of unclear allocation concealment and blinding of personnel or participants. ‡‡ The authors did not report the number of participants who had lesions only on facial or lingual surfaces. This is the number of people at follow-up. §§ Very serious issues of risk of bias exist because of unclear random sequence generation; blinding of participants, personnel, and outcome assessor; and allocation concealment. ¶¶ Serious issues of risk of bias exist because of unclear blinding of outcome assessor and serious imprecision.

eTable 5. Continued

TOTAL NO. OF UNPOOLED STUDIES: 5 RANDOMIZED CONTROLLED TRIALS*,†,‡,§,¶	NO. OF PEOPLE AT FOLLOW-UP/ NO. OF LESIONS AT LONGEST FOLLOW-UP	STUDY ARM (DOSE, DURATION, OR FREQUENCY)	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE
				Without Intervention (%)#	With Intervention	Difference	
Bailey and Colleagues[52]	45/408	10% casein phosphopeptide–amorphous calcium phosphate cream (2 grams morning and evening) and 900 parts per million NaF** mouthrinse (supervised at each visit) and 1,000 ppm NaF dentifrice		70 per 100	86 per 100	16 per 100 more	Low (risk of bias††)
						(From 4 more to 29 more)	
			1.23	50 per 100	62 per 100	12 per 100 more	
			(1.06 to 1.42)			(From 3 more to 21 more)	
				20 per 100	25 per 100	5 per 100 more	
						(From 1 more to 8 more)	
		Placebo cream (2 g morning and evening) and 900 ppm NaF mouthrinse (supervised at each visit) and 1,000 ppm NaF dentifrice					Reference comparator
			Reference comparator	Not estimable	Not estimable	Reference comparator	

eTable 6. Summary of findings: additional follow-up times for nonrestorative treatments for noncavitated lesions on facial or lingual surfaces.

TOTAL NO. OF UNPOOLED STUDIES: 5*,†,‡	PRIMARY, PERMANENT, OR MIXED TEETH	STUDY ARM	RELATIVE RISK (95% CONFIDENCE INTERVAL) AND CERTAINTY IN THE EVIDENCE
Agrawal and Pushpanjali[26]	Mixed	1.23% acidulated phosphate fluoride gel and oral health education (2 doses, baseline and 6 months) Oral health education	1.23% acidulated phosphate fluoride gel and oral health education versus oral health education 12 months: 2.47 (1.95 to 3.13); certainty: moderate (serious issues of risk of bias because of unclear allocation concealment and blinding of personnel or participants)
Autio-Gold and Courts[33]	Primary	5% NaF varnish (baseline and 4 months later, 2 total applications) No intervention	5% NaF varnish versus no intervention 9 months: 2.30 (1.58 to 3.34); certainty: low (very serious issues of risk of bias because of unclear random sequence generation; blinding of participants, personnel, and outcome assessor; and allocation concealment)
Bailey and Colleagues[52]	Mixed	10% casein phosphopeptide−amorphous calcium phosphate cream and 900 parts per million NaF mouthrinse and 1,000 ppm NaF dentifrice (2 grams morning and night for 12 weeks and mouthrinse supervised at each visit) Placebo cream and 900 ppm NaF mouthrinse and 1,000 ppm NaF dentifrice	10% casein phosphopeptide−amorphous calcium phosphate cream and 900 ppm mouthrinse versus 900 ppm mouthrinse 4 weeks: 1.28 (0.97 to 1.68); certainty: low (serious risk of bias because of unclear blinding of outcome assessor and serious imprecision) 8 weeks: 1.12 (0.93 to 1.36); certainty: low (serious risk of bias because of unclear blinding of outcome assessor and serious imprecision) 12 weeks: 1.23 (1.06 to 1.42); certainty: low (serious risk of bias because of unclear blinding of outcome assessor and serious imprecision)

* Source: Agrawal and Pushpanjali.[26] † Source: Autio-Gold and Courts.[33] ‡ Source: Bailey and colleagues.[52]

eTable 7. Summary of findings: nonrestorative treatments for the arrest or reversal of noncavitated lesions on any coronal tooth surface.

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 3 RANDOMIZED CONTROLLED TRIALS*,†,‡ TOTAL NO. OF PARTICIPANTS IN NETWORK: 628 TOTAL NO. OF STUDIES REPORTED NARRATIVELY (UNPOOLED): 4 RANDOMIZED CONTROLLED TRIALS§,¶,#,**	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE	P-SCORE (RANKING)††	INTERPRETATION OF FINDINGS
		Without Intervention (%)‡‡	With Intervention	Difference			
10% Casein Phosphopeptide−Amorphous Calcium Phosphate Paste* (Direct Evidence)		70 per 100	72 per 100	2 per 100 more	Low (risk of bias and imprecision§§)	0.22 (3/4)	May be superior
				(From 7 fewer to 13 more)			
	1.03	50 per 100	52 per 100	2 per 100 more			
	(0.90 to 1.18)			(From 5 fewer to 9 more)			
		20 per 100	21 per 100	1 per 100 fewer			
				(From 2 fewer to 4 more)			
1.23% Acidulated Phosphate Fluoride Gel† (Direct Evidence)		70 per 100	158 per 100	88 per 100 more	Moderate (risk of bias¶¶)	0.89 (1/4)	Superior
				(From 70 more to 107 more)			
	2.25	50 per 100	113 per 100	63 per 100 more			
	(2.00 to 2.53)			(From 50 more to 77 more)			
		20 per 100	45 per 100	25 per 100 more			
				(From 20 more to 31 more)			

* Source: Sitthisettapong and colleagues[57] (12-month follow-up, primary dentition): additional follow-up: 6 months: 10% casein phosphopeptide−amorphous calcium phosphate versus no treatment: relative risk, 1.00 (95% confidence interval, 0.90 to 1.13). † Source: Agrawal and Pushpanjali[26] (12-month follow-up, mixed dentition). ‡ Source: Autio-Gold and Courts[33] (9-month follow-up, primary dentition). § Source: Duarte and colleagues[53] (dentition not reported): 85.4% of noncavitated lesions were arrested in the 0.05% sodium fluoride (NaF) mouthrinse group compared with 85.6% of arrested lesions in the 0.05% NaF mouthrinse and 0.12% chlorhexidine group after 28 days. ¶ Source: Heidmann and colleagues[55] (permanent dentition): in the 0.2% NaF mouth rinse group, 62.5% (n = 270) experienced no progression of noncavitated lesions compared with 68.5% (n = 292) in the placebo mouthrinse group. # Source: Hedayati-Hajikand and colleagues[54] (primary dentition): of 54 people in the probiotic tablet group, 11% (n = 5) of the enrolled patients experienced caries arrest compared with 7% (n = 4) of the 56 participants in the group that received placebo tablets after 1 year. ** Source: Honkala and colleagues[56] (mixed dentition): there was no distinction between cavitated and noncavitated lesions in the study. In the erythritol group, 30.5% (401/1,313) of surfaces showed a decrease in International Caries Detection and Assessment System score compared with 29.8% (456/1,531) in the group receiving sorbitol and 28.3% (449/1,584) in the group receiving xylitol after 3 years of follow-up. †† The lower the value, the higher the position in the ranking. ‡‡ The percentages (20%, 50%, 70%) indicate illustrative baseline probabilities for the arrest or reversal of carious lesions. §§ Serious issues of risk of bias exist because of incomplete outcome data. ¶¶ Serious issues of risk of bias exist because of unclear methods related to allocation concealment and blinding of participants and personnel. ## Very serious issues of risk of bias exist because of unclear methods related to random sequence generation, allocation concealment, and blinding of personnel and participants. *** The studies informing the no-treatment group consist of no treatment, oral health education, placebo paste with 1,000 parts per million fluoride toothpaste, and oral hygiene instructions.[26,33,57]

eTable 7. Continued

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 3 RANDOMIZED CONTROLLED TRIALS*,†,‡ TOTAL NO. OF PARTICIPANTS IN NETWORK: 628 TOTAL NO. OF STUDIES REPORTED NARRATIVELY (UNPOOLED): 4 RANDOMIZED CONTROLLED TRIALS§,¶,#,**	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY IN THE EVIDENCE	P-SCORE (RANKING)††	INTERPRETATION OF FINDINGS
		Without Intervention (%)‡‡	With Intervention	Difference			
5% Sodium Fluoride Varnish† (Direct Evidence)		70 per 100	151 per 100	81 per 100 more	Moderate (risk of bias##)	0.78 (2/4)	Superior
				(From 56 more to 110 more)			
	2.15	50 per 100	108 per 100	58 per 100 more			
	(1.80 to 2.57)			(From 40 more to 79 more)			
		20 per 100	43 per 100	23 per 100 more			
				(From 16 more to 31 more)			
No Treatment*,†,‡,* **					Reference comparator	0.11 (4/4)	Reference comparator
	Reference comparator	Not estimable	Not estimable	Reference comparator			

eTable 8. Summary of findings: nonrestorative treatments for the arrest or reversal of noncavitated and cavitated lesions on root surfaces.

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 7 RANDOMIZED CONTROLLED TRIALS*,†,‡,§,¶,#,** TOTAL NO. OF PARTICIPANTS IN NETWORK: 834†† TOTAL NO. OF UNPOOLED STUDIES: 1 RANDOMIZED CONTROLLED TRIAL‡‡	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY OF THE EVIDENCE	P-SCORE (RANKING)§§	INTERPRETATION OF FINDINGS
		Without Intervention (%)¶¶	With Intervention	Difference			
1% Chlorhexidine plus 1% Thymol Varnish* (Direct Evidence)		70 per 100	117 per 100	47 per 100 more	Very low (risk of bias## and imprecision***)	0.44 (5/6)	May be superior
	1.67	50 per 100	84 per 100	(From 39 fewer to 372 more)			
	(0.44 to 6.31)			34 per 100 more			
		20 per 100	33 per 100	(From 28 fewer to 266 more)			
				13 per 100 more			
38% SDF† Solution **(Direct Evidence)**		70 per 100	134 per 100	(From 11 fewer to 106 more)	Very low (risk of bias††† and imprecision***)	0.49 (4/6)	May be superior
				64 per 100 more			
	1.99	50 per 100	96 per 100	(From 34 fewer to 411 more)			
	(0.52 to 6.87)			46 per 100 more			
		20 per 100	38 per 100	(From 24 fewer to 294 more)			

* Source: Baca and colleagues[59] (12-month follow-up): participants reported a bitter taste when the placebo varnish was used. † Source: Li and colleagues[63] (12-month follow-up): additional follow-ups: 24 months: 38% silver diamine fluoride (SDF) with potassium iodine versus no treatment: relative risk (RR), 2.87 (95% confidence interval [SDF], 1.44 to 5.74); 38% SDF with potassium iodide versus no treatment: RR, 2.99 (95% CI,1.50 to 5.95); 30 months: 38% SDF versus no treatment: RR, 2.00 (95% CI,1.22 to 3.28); 38% SDF with potassium iodide versus no treatment: RR, 2.06 (95% CI, 1.26 to 3.36). ‡ Source: Schaeken and colleagues[65] (12-month follow-up). § Source: Lynch and colleagues[64] (3-month follow-up). ¶ Source: Ekstrand and colleagues[62] (8-month follow-up). # Source: Baysan and colleagues[60] (6-month follow-up): additional follow-ups: 3 months: cavitated, 5,000 ppm versus no treatment: RR, 4.78 (95% CI, 0.60 to 38.20); noncavitated, 5,000 ppm versus no treatment: RR, 3.39 (95% CI, 1.94 to 5.92). ** Source: Ekstrand and colleagues[61] (8-month follow-up). †† We used the total number of participants at 12-month follow-up from Li and colleagues[63]; Schaeken and colleagues[65] did not report loss to follow-up. The number reported is the total number of participants randomly assigned to each group at baseline. In Ekstrand and colleagues,[61] we did not use data from the 1,450 ppm fluoride toothpaste and 5% sodium fluoride (NaF) varnish arm in the network because of the frequency of the 5% NaF varnish not being reported, which accounted for 76 of the 215 participants at baseline. The number reported is the total number of participants in the 5,000 ppm NaF toothpaste arm and control arm at follow-up. Investigators in other studies included in the network reported the total number of participants at follow-up. ‡‡ Source: Brailsford and colleagues[58]: The use of 1% difluorsilane varnish with 1% chlorhexidine and 1% thymol varnish 5 times in 10 months resulted in a 40% increase in caries arrestment (RR, 1.40; 95% CI, 0.97 to 2.00) compared with 1% difluorsilane applied at the same frequency at 1-year follow-up. §§ The lower the value, the higher the position in the ranking. ¶¶ The percentages (20%, 50%, 70%) indicate illustrative baseline probabilities for the arrest of reversal of carious lesions. ## Serious issues of risk of bias exist because of incomplete outcome data and because blinding of the outcomes assessor was unclear. *** Serious issues of imprecision; 95% CI suggests a large harm and a large benefit. ††† Serious issues of bias exist because of incomplete outcome data and unclear methods related to blinding of personnel. ‡‡‡ Serious issues of risk of bias exist because of unclear methods for all risk of bias domains. It is unclear whether patients were blinded and how many were lost to follow-up. §§§ Serious issues of risk of bias exist because of unclear and inadequate methods of random sequence generation and allocation concealment method. In addition, there is no information about blinding of the outcomes assessor, and outcome data are incomplete. Serious issues of inconsistency (I^2 = 88%; $P < .00001$). ¶¶¶ Studies informing the no-treatment group consist of 1,100 ppm dentifrice, soda water with 1,450 ppm dentifrice, 1,450 ppm dentifrice, placebo varnish, and nonfluoride dentifrice.[59,61,63-65]

eTable 8. Continued

TOTAL NO. OF STUDIES IN NETWORK (POOLED): 7 RANDOMIZED CONTROLLED TRIALS[*,†,‡,§,¶,#,**] TOTAL NO. OF PARTICIPANTS IN NETWORK: 834[††] TOTAL NO. OF UNPOOLED STUDIES: 1 RANDOMIZED CONTROLLED TRIAL[‡‡]	RELATIVE RISK (95% CONFIDENCE INTERVAL)	ANTICIPATED ABSOLUTE EFFECT (95% CONFIDENCE INTERVAL)			CERTAINTY OF THE EVIDENCE	P-SCORE (RANKING)[§§]	INTERPRETATION OF FINDINGS
		Without Intervention (%)[¶¶]	With Intervention	Difference			
				18 per 100 more			
38% SDF plus Potassium Iodide[†] Solution **(Direct Evidence)**		70 per 100	165 per 100	(From 10 fewer to 117 more)	Very low (risk of bias[†††] and imprecision[***])	0.61 (3/6)	May be superior
				95 per 100 more			
	2.36	50 per 100	118 per 100	(From 24 fewer to 519 more)			
	(0.66 to 8.42)			68 per 100 more			
		20 per 100	47 per 100	(From 17 fewer to 371 more)			
				27 per 100 more			
5% NaF Varnish[‡] **(Direct Evidence)**		70 per 100	207 per 100	(From 6.8 fewer to 148.4 more)	Very low (risk of bias[‡‡‡] and imprecision[***])	0.64 (2/6)	May be superior
				137 per 100 more			
	2.96	50 per 100	148 per 100	(From 51 fewer to 2,188 more)			
	(0.27 to 32.26)			98 per 100 more			
		20 per 100	59 per 100	(From 37 fewer to 1,563 more)			
				39 per 100 more			
5,000 Parts Per Million Fluoride (1.1% NaF) Toothpaste or Gel[§,¶,#,**] **(Direct Evidence)**		70 per 100	183 per 100	(From 15 fewer to 625 more)	Low (risk of bias and inconsistency[§§§])	0.69 (1/6)	May be superior
				113 per 100 more			
	2.62	50 per 100	131 per 100	(From 34 more to 254 more)			
	(1.49 to 4.63)			81 per 100 more			
		20 per 100	52 per 100	(From 25 more to 182 more)			
				32 per 100 more			
No Treatment[*,†,‡,§,¶,#,**,¶¶¶]				(From 10 more to 73 more)			
	Reference comparator	Not estimable	Not estimable	Reference comparator	Reference comparator	.1335 (6/6)	Reference comparator

Use of Silver Diamine Fluoride for Dental Caries Management in Children and Adolescents, Including Those with Special Health Care Needs

Developed by

American Academy of Pediatric Dentistry

Issued

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Abstract

Background: This manuscript presents evidence-based guidance on the use of 38 percent silver diamine fluoride (SDF) for dental caries management in children and adolescents, including those with special health care needs. A guideline workgroup formed by the American Academy of Pediatric Dentistry developed guidance and an evidence-based recommendation regarding the application of 38 percent SDF to arrest cavitated caries lesions in primary teeth.

Types of studies reviewed: The basis of the guideline's recommendation is evidence from an existing systematic review "Clinical trials of silver diamine fluoride in arresting caries among children: A systematic review." (JDR Clin Transl Res 2016;1[3]:201-10). A systematic search was conducted in PubMed®/MEDLINE, Embase®, Cochrane Central Register of Controlled Trials, and gray literature databases to identify randomized controlled trials and systematic reviews reporting on the effect of silver diamine fluoride and address peripheral issues such as adverse effects and cost. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to assess the quality of the evidence and the evidence- to-decision framework was employed to formulate a recommendation.

Results: The panel made a conditional recommendation regarding the use of 38 percent SDF for the arrest of cavitated caries lesions in primary teeth as part of a comprehensive caries management program. After taking into consideration the low cost of the treatment and the disease burden of caries, panel members were confident that the benefits of SDF application in the target populations outweigh its possible undesirable effects. Per GRADE, this is a conditional recommendation based on low-quality evidence.

Conclusions and practical implications: The guideline intends to inform the clinical practices involving the application of 38 percent SDF to enhance dental caries management outcomes in children and adolescents, including those with special health care needs. These recommended practices are based upon the best available evidence to-date. A 38 percent SDF protocol is included in Appendix II.

KEYWORDS: SILVER DIAMINE FLUORIDE, CLINICAL RECOMMENDATIONS, GUIDELINE, ANTI-INFECTIVE AGENTS, CARIOSTATIC AGENTS, SILVER COMPOUNDS, CARIES, TOPICAL FLUORIDES

Scope and purpose

The guideline intends to inform the clinical practices involving the application of silver diamine fluoride (**SDF**) to enhance dental caries management outcomes in children and adolescents, including those with special health care needs. Silver diamine fluoride in this guideline's recommendation refers to 38 percent SDF, the only formula available in the United States. These recommended practices are based upon the best available evidence to-date. However, the ultimate decisions regarding disease management and specific treatment modalities are to be made by the dental professional and the patient or his/her representative, acknowledging individuals' differences in disease propensity, lifestyle, and environment.

The guideline provides practitioners with easy to understand evidence-based recommendations. The American Academy of Pediatric Dentistry's (**AAPD**) evidence-based guidelines are being produced in accordance with standards created by the National Academy of Medicine (formerly known as the Institute of Medicine) and mandated by the National Guideline Clearinghouse™ (**NGC**), a database of evidence-based clinical practice guidelines and related documents maintained as a public resource by the Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services (USDHHS).

Health intents and expected benefits or outcomes. The guideline is based on analysis of data included in a recent systematic review and meta-analysis[1] and summarizes evidence of the benefits and safety of SDF application in the context of dental caries management, mainly its effectiveness in arresting cavitated

ABBREVIATIONS

AAPD: American Academy of Pediatric Dentistry. CCTs: Controlled clinical trials. EBDC: Evidence-based dentistry committee. EPA: Environmental Protection Agency. GRADE: Grading of Recommendations Assessment, Development and Evaluation. NaF: Sodium fluoride. NGC: National Guideline Clearinghouse. PICO: Population, intervention, control, and outcome. RCTs: Randomized control trials. SDF: Silver diamine fluoride.

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health care needs. Pediatr Dent 2017;39(5):E135-E145.

caries lesions[2 †] in the primary dentition. Its intent is to provide the best available information for practitioners and patientsor their representatives to determine the risks, benefits, and alternatives of SDF application as part of a caries management program. Prevention of new caries lesion development and outcomes in permanent teeth, such as root caries lesion arrest, were not the focus of this guideline; however, because they are of interest and relevant to caries management within the scope of pediatric dentistry, they are mentioned and will be included in future iterations of the guideline as the supporting evidence base increases.

Clinical questions addressed. The panel members used the Population, Intervention, Control, and Outcome (**PICO**)[3] formulation to develop the clinical questions that will aid practitioners in the use of SDF in primary teeth with caries lesions. ***Does the application of SDF arrest cavitated caries lesions as effectively as other treatment modalities in primary teeth?***

Methods

This guideline adheres to the National Academy of Medicine's guideline standards[4] and the recommendations of the Appraisal of Guidelines Research and Evaluation (AGREE) instrument.[5] The guidance presented is based on an evaluation of the evidence presented in a 2016 systematic review published by Gao and colleagues.[1]

Search strategy. Literature searches were used to identify systematic reviews that would serve as the basis of the guideline. Secondly, the results of the searches served as sources of evidence or information on issues related to, but outside the context of, the PICO, such as cost, adverse effects, and patient preferences.

Literature searches were conducted in PubMed® /MEDLINE, Embase®, Cochrane Central Register of Controlled Trials, gray literature, and trial databases to identify systematic reviews and randomized controlled trials of SDF. Search results were reviewed in duplicate at both the title and abstract and the full-text level when warranted. Disagreements were resolved by consensus;if agreement could not be reached, the AAPD Evidence-Based Dentistry Committee (**EBDC**) overseeing the workgroup was consulted to settle the question. A detailed description of the search strategies is presented in Appendix I.

Inclusion and exclusion criteria. The criteria used to identify publications for use in the guideline were determined by the clinical PICO question. See Appendix I for search strategies. Publications which addressed the use of SDF to arrest caries lesions in primary teeth, regardless of language, merited full-text review; in vitro studies and studies of the use of SDF outside of the guideline's stated outcomes were excluded. No new randomized controlled trials were identified that warranted updating the meta-analysis found in the systematic review[1] selected as the basis for this guideline.

Assessment of the evidence. The main strength of this guideline is that it is based on a systematic review of prospective randomized and controlled trials of SDF[1]. Evidence was assessed via the Grading of Recommendations Assessment, Develop- ment, and Evaluation (**GRADE**) approach[6], a widely adopted and peer reviewed system of evaluating study quality (Table 1). The guideline recommendation is based on the meta-analysis offour controlled trials (three randomized), extracted in duplicate,from a systematic review of SDF[1]. Randomized (**RCTs**) and controlled clinical trials (**CCTs**) offer the highest level of clinical evidence; therefore, a recommendation based on a systematic review and meta-analysis of graded RCTs/CCTs provides more reliable and accurate conclusions that can be applied towards patient care.

This guideline is limited by the small number of RCTs evaluating SDF, the heterogeneity of the included trials, and selection bias that may have been introduced by possibly poor sequence generation[7,8] and selective reporting by one study[7]. Weaknesses of this guideline are inherent to the limitations found in the systematic review[1] upon which this guideline is based. Major limitations of the supporting literature include lack of calibration and/or evidence of agreement for examiners assessing clinical outcomes and unclear definitions or inconsistent criteria for caries lesion activity.[9,10] Arguably, without a valid and reliable method to determine lesion activity at baseline and follow-up, misclassification bias is possible, especially because clinicians cannot be blinded with regard to SDF application (due to the dark staining).[9,10] The absence of rigorous caries detection and activity measurement criteria in the reviewed liter-ature can decrease the validity of the reported results.[9,10] Other

† *A caries lesion is a detectable change in the tooth structure that results from the biofilm-tooth interactions occurring due to the disease caries. It is the clinical manifestation (sign) of the caries process.*

Table 1. QUALITY OF EVIDENCE GRADES†

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

† Quality of evidence is a continuum; any discrete categorization involves some degree of arbitrariness. Nevertheless, advantages of simplicity, transparency, and vividness outweigh these limitations.

reviewers of the systematic review[1] noted similar and additional limitations.[9,10]

Formulation of the recommendations. The panel formulated this guideline collectively via surveys, teleconferences, and electronic communications from January 2017–August 2017. The panel used the evidence-to-decision framework in an iterative manner to formulate the recommendations. Specifically, the main methods used were discussion, debate, and consensus seeking.[11] To reach consensus, the panel voted anonymously on all contentious issues and on the final recommendation. GRADE was used to determine the strength of the evidence.[12]

Understanding the recommendations. GRADE rates the strength of a recommendation as either strong or condi- tional. A strong recommendation "is one for which guideline panel is confident that the desirable effects of an intervention outweigh its undesirable effects (strong recommendation for an intervention) or that the undesirable effects of an intervention outweigh its desirable effects (strong recommendation against an intervention)."[6] A strong recommendation implies most patients would benefit from the suggested course of action (i.e., either for or against the intervention). A conditional recommendation "is one for which the desirable effects probably outweigh the undesirable effects (conditional recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (conditional recommendation against an intervention), but appreciable uncertainty exists."[6] A conditional recommendation implies that not all patients would benefit from the intervention. The individual patient's circumstances, preferences, and values need to be assessed more than usual. Practitioners need to allocate more time for consultation along with explanation of the potential benefits and harms to the patients and their caregivers when recommendations are rated as conditional. Practitioners' expertise and judgment as well as patients' and their caregivers' needs and preferences establish the suitability of the recommendation to individual patients. The strength of a recommendation presents different implications for patients, clinicians, and policy makers (Table 2).

Recommendations

The SDF panel supports the use of 38 percent SDF for the arrest of cavitated caries lesions in primary teeth as part of a comprehensive caries management program. (***Conditional recommendation, low-quality evidence***)

Summary of findings

The recommendation is based on data from a meta-analysis of data extracted from RCTs and CCTs of SDF efficacy with various follow-up times and controls (Table 3). Based on the pooled estimates of SDF group, approximately 68 percent (95 percent confidence interval [**95% CI**]=9.7 to 97.7) of cavitated caries lesions in primary teeth would be expected to be arrested two years after SDF application (with once or twice a year application). Using data with longest follow-up time (at least 30 months follow-up; n=2,567 surfaces from one RCT[7] and one CCT[8]), SDF had 48 percent higher (95% CI=32 to 66) success rate in caries lesion arrest compared to the controls (76 percent versus 51 percent arrested lesions, in absolute terms). In other words, 248 more cavitated caries lesions would be expected to arrest by treatment with SDF compared to control treatments, per 1000 surfaces after at least 30 months follow- up. Considering the stratum with most data (n=3,313 surfaces from three RCTs and one CCT, with follow-up of 24 monthsor more), similar estimates of relative and absolute efficacy were produced (i.e., RR 1.42 [95% CI=1.17 to 1.72]) and 72 percent versus 50 percent arrested lesions, in absolute terms. Other follow-up and application frequency strata are listed in the summary of findings (Table 3). The range of estimates of SDF efficacy between the included trials was categorically wide. Rates of arrest on untreated groups may seem unusually high, and this may be due to background fluoride exposure. In oneof the trials[7], all participants (i.e., both the SDF-treated and control children) received 0.2 percent sodium fluoride (**NaF**) rinse every other week in school, while in other trials, children were either given fluoride toothpaste[13] or reported use of fluoridetoothpaste[8]. The panel determined the overall quality of the

Table 2. IMPLICATIONS OF STRONG AND CONDITIONAL RECOMMENDATIONS FOR DIFFERENT USERS OF GUIDELINES

	Strong recommendation	**Conditional recommendation**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policymaking will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Reprinted with permission. GRADE Handbook: Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Update October 2013. Available at: "http://gdt.guidelinedevelopment.org/app/handbook/handbook.html".

evidence for this comparison was low or very low, owing to serious issues of risk of bias (unclear method for randomization, selective reporting, and high heterogeneity) in the included studies. No studies were identified regarding the arresting effect of SDF on cavitated caries lesions in adult patients. The panel suggests that similar treatment effects may be expected for other age groups, but the lack of evidence informing this recommendation restrained the panel from providing an evidence-based recommendation.

The panel made a conditional recommendation regarding the use of SDF for the arrest of cavitated caries lesions in primary teeth as part of a comprehensive caries management program. After taking in consideration the low cost of the treatment and the disease burden of caries, panel members were confident that the benefits of SDF application in the target populations outweigh its possible undesirable effects. Specifically:

1. Untreated decay in young children remains a challenge, from clinical and public health standpoints, in the U.S. and worldwide.[14] It confers significant health and quality of life impacts to children and their families, and it is marked by pronounced disparities.[15]
2. Surgical-restorative work in young children and those with special management considerations (e.g., individuals with special health care needs) often requires advanced pharmacologic behavior guidance modalities (e.g., sedation, general anesthesia). These pathways of care have additional health risks and limitations (e.g., possible effects on brain development in young children, mortality risks[16]), and often are not accessible, at all or in a timely manner.[17-19] The U.S. Food and Drug Administration has issued a warning "that repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than three may affect the development of children's brains."[20]
3. The cost of managing severe early childhood caries is disproportionally high, especially when hospitalization is necessary. The need to treat children in a hospital setting with general anesthesia is a common scenario in the U.S. and other countries.[21] Studies report that children from the less-affluent regions have higher dental surgeryrates than those from more-affluent communities (25.7vs. 6.9 per 1,000)[17], which results in an economic burden for communities already impacted by the effects of poverty-related health problems.[19,22]

Table 3. SUMMARY OF FINDINGS: EVIDENCE FOR THE RELATIVE AND ABSOLUTE EFFICACY OF SDF APPLICATION COMPARED TO NO SDF FOR THE ARREST OF CAVITATED CARIES LESIONS ON PRIMARY TEETH*

Patient or population: Children and adolescents with cavitated caries lesions on primary teeth
Intervention: SDF (various periodicities)
Comparison: No SDF (various controls, including active agents and treatment)
Outcome: Caries arrest in primary teeth

Follow-up time; N surfaces (studies)	Relative efficacy, RR (95% CI)	Absolute estimates, % arrested lesions (95% CI) Ω		Quality assessment
		No SDF (other active controls or no treatment)	SDF	
24 months; 746 surfaces (2 RCTs: Yee et al., 2009 & Zhi et al., 2012) ∨	**RR 1.45** (0.79 to 2.66)	47.9% (3.8 to 95.6) [A]	**68.0%** (9.7 to 97.7)	⊕OOO VERY LOW [a,b,c]
≥24 months; 3313 surfaces (3 RCTs: Llodra et al., 2005, Yee et al., 2009 & Zhi et al., 2012., 1 CCT: Chu et al., 2002) ς	**RR 1.42** (1.17 to 1.72)	49.6% (28.8 to 70.5)[C]	**72.4%** (48.0 to 88.1)	⊕OOO VERY LOW [a,d,e]
≥30 months; 2567 surfaces (1 CCT: Chu et al., 2002 & 1 RCT: Llodra et al., 2005.) Ξ	**RR 1.48** (1.32 to 1.66)	50.8% (32.5 to 69.0)[B]	**76.4%** (52.1 to 90.6)	⊕⊕OO LOW [a,b]
semi-annual application ≥24 months; 1784 surfaces (2 RCTs: Llodra et al., 2005 & Zhi et al., 2012)	**RR 1.25** (0.99 to 1.58)	72.4 % (47.2 to 88.5) [A]	**87.7%** (80.9 to 92.4)	⊕OOO VERY LOW [a,d,e]

CCT= Controlled clinical trials; CI= Confidence interval; RCTs= Randominzed control trials; RR= Relative risks.

* Rates of arrest on untreated groups may seem unusually high, and this may be due to background fluoride exposure. In one of the trials[7], all participants (i.e., both the SDF-treated and control children) received 0.2 percent NaF rinse every other week in school, while in other trials, children were either given fluoride toothpaste[13] or reported use of fluoride toothpaste[8].

∨ Yee is once a year application of SDF, and Zhi is once a year vs. twicea year.

ς Chu is once a year application of SDF, Llodra is twice a year, Yee is oncea year, and Zhi is once a year vs. twice a year.

Ξ Chu is once a year application of SDF, Llodra is twice a year.

Ω The pooled effect estimates and confidence intervals for the relative risk and absolute percentages were derived from random effect modeling.

A Comparisons included glass ionomer and no treatment.

B Comparisons included no treatment.

C Comparisons included both A and B.

a At least one domain had 'unclear' risk of bias assessment.

b High heterogeneity.

c Wide confidence interval of the relative risk.

d Very high heterogeneity.

e Wide confidence interval.

4. With caries lesion arrest rates upwards of 70 percent (i.e., higher than other comparable interventions), SDF presents as an advantageous modality. Besides its efficacy, SDF is favored by its less invasive (clinically and in termsof behavior guidance requirements) nature and its inexpensiveness.
5. The undesirable effects of SDF (mainly esthetic concerns due to dark discoloration of carious SDF-treated dentin) are outweighed by its desirable properties in most cases, while no toxicity or adverse events associated with its use have been reported.

In sum, the panel felt confident that a conditional recommendation was merited because, although a majority of patients would benefit from the intervention, individual circumstances, preferences, and values need to be assessed by the practitioner after explanation and consultation with the caregiver.

Research considerations. Research is needed on the use of SDF to arrest caries lesions in both primary and permanent teeth. The panel urges researchers to conduct well-designed randomized clinical trials comparing the outcomes of SDF to other treatments for the arrest of caries lesions in primary and permanent teeth.

Potential adverse effects. Silver diamine fluoride contains approximately 24-28 percent (weight/volume) silver and 5-6 percent fluoride (weight/volume).[23] Exposure to one drop of SDF orally would result in less fluoride ion content than is present in a 0.25 mL topical treatment of fluoride varnish. The exact amount of silver and fluoride present in one drop ofSDF is determined by the specific gravity of the liquid and the dropper used. More studies are required to determine that amount, given the stability of the product manufactured and packaged in the U.S.

In published clinical trials encompassing over 4,000 young children worldwide, exposure to manufacturer's recommended amounts of SDF has not resulted in any reported deaths or systemic adverse effects.

Oral absorption can include absorption in mucous membranes in the mouth and the nasal cavity. The short-term health effects in humans as a result of exposure to water or food containing specific levels of silver are unknown. The Environmental Protection Agency (**EPA**) suggests levels of silver in drinking water not to exceed 1.142 mg/L (1.42 ppm). Silver diamine fluoride should not be used in patients with an allergy to silver compounds.[24]

The main disadvantage of SDF is its esthetic result (i.e., permanently blackens enamel and dentinal caries lesions and creates a temporary henna-appearing tattoo if allowed to come in contact with skin). Skin pigmentation is temporary since the silver does not penetrate the dermis. Desquamation of the skin with pigmentation occurs when keratinocytes are shedover a period of 14 days.[25] Silver diamine fluoride also permanently stains most surfaces (e.g., counters, clothing) with which it comes into contact.

Guideline implementation. This guideline will be published in the AAPD's Reference Manual and the journal, *Pediatric Dentistry*. Social media, news items, and presentations will beused to notify AAPD members about the new guideline.

This guideline will be available as an open access publication on the AAPD's website. Patient education materials are being developed and will be offered in the AAPD's online bookstore. See Appendix II for practical SDF guidance and the Resource Section of the AAPD Reference Manual for a SDF chairside guide.[26]

Cost considerations. Silver diamine fluoride is an effective and inexpensive means of arresting cavitated caries lesions in primary teeth.[27] It is inexpensive due to the low cost of materials and supplies and relatively short chair time required for application. Nevertheless, an empirical cost analysis discussionfor SDF would need to address the several additional considera-tions and parameters. First, given the wide array of surgical andnon-surgical management approaches for cavitated caries lesionsin the primary dentition, agreement on consensus endpointsand, therefore, total cost is challenging and controversial. Second, cost should include patient/family and practitioner time, health care services utilized, and cost of non-health impacts, if any. Third, SDF economic analyses are likely best approached via a cost-utility framework, wherein expenditures are juxtaposed to quality-adjusted or disease-free years. To illustrate the importance of defining a consensus treatment endpoint, in this scenariodisease-free years can be interpreted as caries inactive, no surgical intervention needed, or pain-free years. Finally, the economic benefits of SDF application must be considered in the context of pathways of clinical care (i.e., disease management) and account, among other factors, for the risks and costs associated with advanced behavior management techniques (e.g., indicated surgical-restorative work may require sedation or general anesthesia in some cases), families' preferences, and opportunity costs (e.g., time investment beyond the direct costs).

Recommendation adherence criteria

Guidelines are used by insurers, patients, and health care practitioners to determine quality of care. In principle, following best practices and guidelines is believed to improve outcomes and reduce inappropriate care.[28] Therefore, measuring adherence to oral health-related guidelines is key and can serve as manifestation of the dental community's role as a "responsible steward oforal health."[29] Though measurement of oral health outcomes is in its early days at both system and practice levels, system-level performance measures for some oral health areas have been developed by the Dental Quality Alliance of the American Dental Association in partnership with the AAPD and other dental organizations. The goals of professional accountability, transparency, and oral health care quality can be furthered through these measures.

Workgroup. In December 2016, the AAPD's Board of Trustees approved a panel nominated by the EBDC to develop a new evidence-based clinical practice guideline on SDF. The panel consisted of general and pediatric dentists in public and private practice involved in research and education; the stakeholders consisted of representatives from general dentistry, dental hygiene, governmental and non-governmental agencies, and international and specialty dental organizations.

Stakeholders and external review. This guideline was reviewed by external and internal stakeholders continuously from the beginning of the process until the formulation of the guideline. Stakeholders were invited to take part in anonymous surveys to determine the scope and outcomes of the guideline, bringing in points of view from different geographical regions, dental specialties, and patient advocates. Comments also were sought on the draft of the guideline. All stakeholder comments were taken into consideration, addressed, and acted upon as appropriate per group deliberation. Additional feedback from stakeholders is expected after publication and dissemination of the guideline.

Intended users. The target audience for this guideline is general dentists, pediatric dentists, pediatricians, and family practice physicians. Public and private payors will benefit from reviewing the evidence for coverage decisions regarding SDF use, and patients and patient advocates may find it useful as a reference for current available treatments for caries management. The target populations include children and adolescents, including those with special health care needs.

Guideline updating process. The AAPD's EBDC will monitor the biomedical literature to identify new evidence that may impact the current recommendations. These recommendations will be updated five years from the time the last systematic search, unless the EBDC determines that an earlier revision or update is warranted.

References appear after Appendices.

Appendices

Appendix I—Search strategies

PubMed® (MEDLINE)– no date limit

Search #1. 145 results

cariestop OR "silver diamine fluoride"[Supplementary Concept] OR "silver diamine" OR "silver diammine" OR "diamine fluoride" OR "diammine fluoride" OR saforide OR "Riva star"

Search #2. 6589771 results

(randomized controlled trial[pt] OR controlled clinical trial [pt] OR randomi*[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic" [MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses" [tw]) NOT (animals [mh] NOT humans [mh])

Search #3. 14 results

#1 and #2

Search #4. 410530 results

(systematic[sb] OR meta-analysis[pt] OR meta-analysis as topic[mh] OR meta-analysis[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met analy*[tw] OR research overview*[tiab] OR collaborative review*[tiab] OR collaborative overview*[tiab] OR systematic review*[tiab] OR comparative efficacy[tiab] OR comparative effectiveness[tiab] OR outcomes research[tiab] OR systematic overview*[tiab] OR methodological overview*[tiab] OR methodologic overview*[tiab] OR methodological review*[tiab] OR methodologic review*[tiab] OR quantitative review*[tiab] OR quantitative overview*[tiab] OR quantitative synthes*[tiab] OR pooled analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data synthes*[tiab] OR data extraction[tiab] OR data abstraction*[tiab] OR mantel haenszel[tiab] OR peto[tiab] OR dersimonian[tiab] OR dersimonian[tiab] OR fixed effect*[tiab] OR "Cochrane Database Syst Rev"[Journal])

Search #5. 14 results

#1 and #4*

Search #6. 890576 results

("Economics"[Mesh] OR "Cost of Illness"[Mesh] OR "Cost Savings"[Mesh] OR "Cost Control"[Mesh] OR "Cost-Benefit Analysis"[Mesh] OR "Health Care Costs"[Mesh] OR "Direct Service Costs"[Mesh] OR "economics"[Subheading] OR cost))

Search #7. 8 results

#1 AND #6

* *Search results vetted in duplicate using an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses checklist.*

Appendix II—Practical guidance*

*** Silver diamine fluoride in this guideline's recommendation refers to 38 percent SDF, the only formula available in the United States.**

Setting

Practitioners must first consider the current standard of care of the setting where SDF therapy is intended for use. Silver diamine fluoride is optimally utilized in the context of a chronic disease management protocol, one that allows for the monitoring of the clinical effectiveness of SDF treatment, disease control, and risk assessment.

Practical recommendation: Know the setting where SDF is to be used to be consistent with goals of patient-centered care.

Indications and usage

The following scenarios may be well-suited for the use SDF:

- High caries-risk patients with anterior or posterior active cavitated lesions.
- Cavitated caries lesions in individuals presenting with behavioral or medical management challenges.
- Patients with multiple cavitated caries lesions that may not all be treated in one visit.
- Difficult to treat cavitated dental caries lesions.
- Patients without access to or with difficulty accessing dental care.
- Active cavitated caries lesions with no clinical signs of pulp involvement.

Practical recommendation: SDF is a valuable caries lesion–arresting tool that can be used in the context of caries management. Evaluate carefully which patients/teeth will benefit from SDF application.

Preparation of patients and practitioners

Informed consent, particularly highlighting expected staining of treated lesions, potential staining of skin and clothes, and need for reapplication for disease control, is recommended.

The following practices are presented to support patient safety and effectively use SDF:

- Universal precautions.
- No operative intervention (e.g., affected or infected dentin removal) is necessary to achieve caries arrest.[8]
- Protect patient with plastic-lined bib and glasses.
- Cotton roll or other isolation as appropriate.
- Use a plastic dappen dish as SDF corrodes glass and metal.
- Carefully dispose of gloves, cotton rolls, and micro brush into plastic waste bag.

Application

Carious dentin excavation prior to SDF application is not necessary.[8] Caries dentin excavation may reduce proportion of arrested caries lesions that become black, and may be considered for esthetic purposes.[30] Functional indicator of effectiveness (i.e., caries arrest) is when staining on dentinal carious surfaces is visible.

The following steps may vary depending on differing practices, settings, and patients:

- Remove gross debris from cavitation to allow better SDF contact with denatured dentin.
- Minimize contact with gingiva and mucous membranes to avoid potential pigmentation or irritation; consider applying cocoa butter or use cotton rolls to protect surrounding gingival tissues, with care to not inadvertently coat the surfaces of the carious lesion.
- Dry with a gentle flow of compressed air (or use cotton rolls/gauze to dry) affected tooth surfaces.
- Bend micro sponge brush, dip and dab on the side of the dappen dish to remove excess liquid before application;[24] apply SDF directly to only the affected tooth surface.
- Dry with a gentle flow of compressed air for at least one minute.
- Remove excess SDF with gauze, cotton roll, or cotton pellet to minimize systemic absorption.[4] Continue to isolate site for up to three minutes when possible.

Practical recommendation: No need for surgical intervention (e.g., dentin excavation). SDF application is minimally invasive and easy for the patient and the practitioner. It may be desirable for the caries lesion to be free of gross debris for SDF to have maximum contact with the affected dentin surface.

Application time

An application time of one minute, drying with a gentle flow of compressed air, is recommended. Clinical studies that report application times range from 10 seconds to three minutes. A current review states that application time in clinical studies does not correlate to outcome.[24] More studies are needed to confirm an ideal protocol.

Practical recommendation: Ideal time of application should be one minute, using a gentle flow of compressed air until liquid is dry. When using shorter application periods, monitor carefully at post-op and re-care to evaluate arrest and consider re-application.

Post-operative instructions

No postoperative limitations are listed by the manufacturer. Eating and drinking immediately following application is acceptable. Patients may brush with fluoridated toothpaste as per regular routine following SDF application.

Several SDF clinical trials recommended no eating or drinking for 30 minutes – one hour.[13,31,32] As patients are used to these recommendations for in-office topical fluoride applications, the recommendation may not be unreasonable to patients, and it may allow for better arrest results. More clinical studies are needed to establish best practices.

Application frequency

The effectiveness of one-time SDF application in arresting dental caries lesions ranges from 47 percent to 90 percent, depending on the lesion size and the location of the tooth and the lesion. One study showed that anterior teeth had higher rates of caries lesion arrest than posterior teeth.[33] The effectiveness of caries lesion arrest, however, decreases over time. After a single application of 38 percent SDF, 50 percent of the arrested surfaces at six months had reverted to active lesions at 24 months.[13]

Reapplication may be necessary to sustain arrest.[8,31-33] Annual application of SDF is more effective in arresting caries lesions than application of five percent sodium fluoride varnish four times per year.[30] Increasing frequency of application can increase caries arrest rate. Biannual application of SDF increased the rate of caries lesion arrest compared to annual application.[33] Studies that had three times per year applications showed higher arrest rates.[7,31,33,34] Frequency of application after baseline has been suggested at three month follow up, and then semiannual recall visits over two years.[24] One option is to place SDF on active lesions in conjunction with fluoride varnish (**FV**) on the rest of the dentition, or alternate SDF on caries lesions and FV on the rest of the dentition at three months interval to achieve arrest and prevention in high risk individuals.[35] Another study recommends one month post operative evaluation of treated lesions with optional reapplication as required to achieve arrest of all targeted lesions.[35] Individuals with high plaque index and lesions with plaque present display lower rates of arrest. Addressing other risk factors like presence of plaque may increase the rate of successful treatment outcomes.[33]

Practical recommendation: If the setting allows, monitor caries lesion arrest after 2-4 week period and consider reapplication as necessary to achieve arrest of all targeted lesions. Provide re-care monitoring based on patient's disease activity and caries risk level (every three, four, or six months). Carefulmonitoring and behavioral intervention to reduce individualrisk factors should be part of a comprehensive caries manage- ment program that aims not only to sustain arrest of existing caries lesions, but also to prevent new caries lesion development.

Adverse reactions

No severe pulpal damage or reaction to SDF has been reported.[7,36-38] However, SDF should not be placed on exposed pulps. Teeth with deep caries lesions should be closely monitored clinically and radiographically.

Serum concentration of fluoride following SDF application per manufacturer recommendations posed little toxicity riskand was below EPA oral reference dose in adults.[39]

The following adverse effects have been noted in the literature:

- Metallic/bitter taste.[24]
- Temporary staining to skin which resolves in 2-14 days.[24]
- Mucosal irritation/lesions resulting from inadvertent contact with SDF, resolved within 48 hours.[7]

Esthetics

The hallmark of SDF is a visible dark staining that is a sign of caries arrest on treated dentin lesions. This dark discoloration is permanent unless restored. A recent study that assessed parental perceptions and acceptance of SDF based on the staining found that staining on posterior teeth was more acceptable than on anterior teeth.[40] Although staining on anterior teeth was perceived as undesirable, most parents preferred this option to avoid the use of advanced behavioral guidance techniques such as sedation or general anesthesia to deliver traditional restorative care. It was also found that about one-third of parents found SDF treatment unacceptable under any circumstance due to esthetic concerns. To identify those patients, a thorough in- formed consent, preferably with photographs that show typical staining, is imperative.[40] To improve esthetics, once the disease is controlled and patient's circumstances allow, treated andnow-arrested cavitated caries lesions can be restored.[35]

Other considerations

- Coding – D1354; Reimbursement for this procedure varies among states and carriers. Third-party payors' coverage isnot consistent on the use of this code per tooth or per visit. Practitioners are cautioned to check insurance coverage for this code as it is transitioning in most areas.
- Caries arrest is more likely on the maxillary anterior teeth[8,31] and buccal/lingual smooth surfaces[31].
- Pretreatment of dentin with SDF does not adversely affect bond strength of resin composite to dentin.[41,42]

References on next page.

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RESEARCH REPORTS
Clinical

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The Short-term Effects of Diammine Silver Fluoride on Tooth Sensitivity: a Randomized Controlled Trial

ABSTRACT

Tooth sensitivity is a common clinical problem. This multi-center randomized clinical trial assessed the effectiveness and safety of topical diammine silver fluoride. From two sites (Lima and Cusco, Peru), 126 adults with at least one tooth sensitive to compressed air were randomly assigned to either the experimental treatment or sterile water, and pain was assessed by means of a 100-mm visual analogue scale at 24 hours and 7 days. The diammine silver fluoride reduced pain at 7 days at both sites. At the Lima site, the average change in pain scores between baseline and day 7 for the silver fluoride group was -35.8 (SD = 27.7) mm *vs.* 0.4 (SD = 16.2) mm for the control group ($P < 0.001$). In Cusco, the average change in pain scores for the silver fluoride group was –23.4 (SD = 21.0) mm and -5.5 (18.1) mm for the controlgroup ($P = 0.002$). No tissue ulceration, white changes, or argyria was observed. A small number of participants in the silver fluoride group experienced a mild but transient increase in erythema in the gingiva near the tooth. No changes were observed in the Gingival Index. We concluded that diammine silver fluoride is a clinically effective and safe tooth desensitizer.

KEY WORDS: tooth sensitivity, silver diamine fluoride, diammine silver fluoride, silver diammine fluoride, fluorides, topical.

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INTRODUCTION

Tooth sensitivity to various stimuli, including cold air, has been explained by hydrodynamic changes within the dentinal tubules that activate intradental nerves (Markowitz and Pashley, 2008). Incidence is thought to be increasing. The etiology can be tooth wear, aggressive oral hygiene, and diet. Successful treatments physically block dentinal tubules (Arends *et al*., 1997).

Sodium fluoride varnish and fluoride solutions and gels have been shown to reduce sensitivity (Thrash *et al*., 1992; Ritter *et al*., 2006). However, there is continuing interest in finding effective treatments. Nevertheless, recent studies have designs that are weak or statistically underpowered (Erdemir *et al*., 2010; Jalali and Lindh, 2010).

The purpose of this study was to assess the clinical effectiveness and safety of topical diammine silver fluoride as a tooth desensitizer in adults.

METHODS

Design

This is a randomized clinical trial with two groups (Fig. 1). The study tested application of diammine silver fluoride in a single visit, because previous unpublished work had shown that a single application forms insoluble precipitates with calcium and phosphate that physically block dentinal tubules. The International Clinical Trials Registry number is NCT01063530.

Study Sites

The study was conducted in two sites, Lima and Cusco, Peru.

Participants

To be included, a participant must have at least one vital cuspid or premolar with a buccal cervical defect and clinical hypersensitivity in response to compressed air with a score ≥ 15 on a visual analogue scale (VAS) for pain. The individual will have had generally healthy gum tissue surrounding this tooth and no ulceration and no leukoplakia in this gingival tissue.

Candidates were excluded if they were using any type of tooth desensitizer, had received a fluoride varnish treatment within the preceding month, or were taking prescription medications, aspirin, or non-steroidal anti-inflammatory drugs; women who were pregnant were also excluded. Individuals using smokeless tobacco or chewing coca leaves were excluded. Individuals with known sensitivity to silver or other heavy-metal ions were excluded.

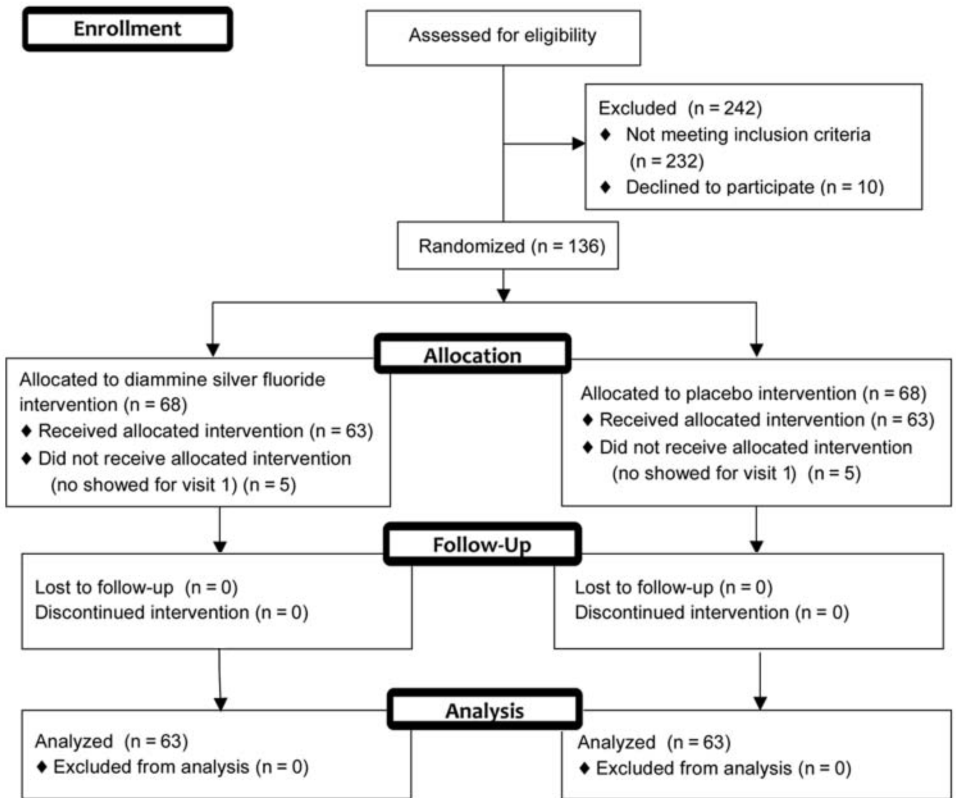

Figure 1. Flow chart for clinical trial sites combined.

Participants were recruited from the patient populations of Cayetano University School of Dentistry and the private dental practices of the investigators in Lima and Cusco between January and June, 2010, and were offered a small financial incentive for participation.

The Institutional Review Board of Universidad Peruana Cayetano Heredia approved the protocol, and the informed consent of all participants was obtained.

Treatment Conditions

Diammine silver fluoride [$Ag(NH_3)_2F$, CAS RN 33040–28–7, Saforide, Toyo Seiyaku Kasei Co. Ltd. Osaka, Japan] was used. It is clear and colorless, with a weak odor of ammonia. According to the manufacturer, the solution includes not less than 24.4 w/v% and not more than 26.8 w/v% of silver (Ag), not less than 5.0 w/v% and not more than 5.9 w/v% of fluorine (F). Diammine silver fluoride is also referred to as silver diammine fluoride, silver diamine fluoride, or silver fluoride.

Assignment to Conditions

Participants were randomly assigned to treatment with diammine silver fluoride or sterile water. The randomization was stratified on study site and baseline tooth sensitivity score (< 37 and ≥ 37) to a five-second blast of pressurized air at 2 cm distance from the tooth, and blocking was used to ensure that the two groups would be balanced across the study period and within each stratum. The stratifi- cation at 37 was chosen from the literature (Ritter *et al*., 2006). A pre-test of the VAS with 10 individuals confirmed the mean response in this range. Block sizes were equal to 2 or 4, and were chosen randomly with 2/3 and 1/3 probability, respectively. The assignments were generated by the project statistician, using the "sample" function of R statistical software (Version 2.7.1, The R Foundation for Statistical Computing, 2008). The assignments were recorded on slips of paper numbered consecutively within each stratum and then placed inside sealed envelopes sequentially numbered by stratum. The statistician retained the master list until all the data were analyzed. The clinician would open the envelope and apply the agent. The agents (active or control) were packaged in identical dark glass bottles labeled as A or B. The packaging was done at Cayetano University.

Clinical Procedure

The clinical procedure was that a disposable microbrush was dipped into a drop of the diammine silver fluoride or the control and then applied to the surface for 1 sec. Then the surface was gently air-dried and the procedure repeated.

Measures

Primary Outcome-Clinical

Reduction of pain (tooth sensitivity)—The teeth were isolated with gauze, and participants were asked to report tooth pain on a 100-mm visual analogue scale (VAS; Ritter *et al*., 2006)before treatment and after treatment with a five-second blast of pressurized air at 2 cm distance from the tooth. The VAS was anchored with "no pain" and "intolerable pain". The follow-up test was repeated at 24 hrs and 7 days later. A single person in each site conducted the assessment in Spanish. The scale was pre-tested to ensure that the descriptors were translated properly.

Safety

Damage to gingiva—Tissues were photographed before treatment to establish the normal baseline condition. A single examiner examined gingival tissues surrounding each treated tooth immediately after treatment, and at 24 hrs and 7 days later. The primary safety measure is erythema. It was assessed visually

Table 1. Tooth Sensitivity by Study Site and Condition

Study Site	Time	Condition		
Lima		Silver Fluoride (N = 37)	Control (N = 34)	
		Mean VAS (SD) [Range]	Mean VAS (SD) [Range]	*P*-value*
	Baseline	57.3 (26.7) [17, 99]	49.3 (19.3) [15, 84]	0.16
	24 hrs	28.2 (22.1) [2, 75]	52.1 (22.8) [16, 89]	
	Change from baseline	-29.1 (27.5) [-94, 10]	2.6 (15.3) [-44, 32]	< 0.0001
	7 days	21.5 (23.0) [1, 78]	49.9 (21.2) [9, 85]	
	Change from baseline	-35.8 (27.7) [-97, 12]	0.4 (16.2) [-38, 33]	< 0.0001
Cusco		Silver Fluoride (N = 26)	Control (N = 29)	
		Mean VAS (SD) [Range]	Mean VAS (SD) [Range]	*P*-value
	Baseline	51.7 (20.5) [22, 92]	51.6 (22.4) [16, 99]	0.98
	24 hrs	45.2 (24.1) [11, 87]	50.6 (22.0) [15, 95]	
	Change from baseline	-6.5 (13.1) [-34, 22]	-1.0 (11.7) [-37, 20]	0.11
	7 days	28.3 (21.8) [2, 94]	46.1 (24.4) [3, 92]	
	Change from baseline	-23.4 (21.0) [-56, 24]	-5.5 (18.1) [-77, 18]	0.0015

*Two-sample *t* test (unequal variances).

with the use of a standard dental light. Erythema (red changes) was rated on a 1 to 3 scale, where 1 is no redness, 2 is redness with bleeding on probing, and 3 is a severe change. The Gingival Index (Löe, 1967) was used to measure gingival inflammation in the mouth overall. White changes, ulceration, and staining were secondary measures. Changes were rated as present or absent. Examiners were trained to criteria using pho-tographs and clinical cases. Intra- and inter-examiner reliability was established in 15 cases, and intraclass correlation was used to assess reliability. All intraclass correlations exceeded 0.8.

Data Analysis Plan

The data from the two sites were analyzed. To confirm reduction in pain, we calculated average difference scores between pre- and post-treatment VAS scores for each individual for each time-point (24 hrs and 7 days after treatment), and *t* tests were used to compare changes. The primary end point was at 7 days. Generalized estimating equations (GEE) linear regression was used in a secondary analysis to compare the reduction in pain across the 3 time-points, where the outcome is pain at the 3 time-points, the baseline pain is a covariate, and robust standard errors are used to account for multiple observations *per* participant and heteroscedasticity (Hardin and Hilbe, 2002). In addition, separate analyses of covariance were done at each time-point to compare the reduction in pain due to the active treatment between the two study sites, where the outcome is the pain at a particular time-point, baseline pain was entered as a covariate, and treatment and site, as well as a treatment-group-by-site interaction, were entered as factors.

We used Fisher's Exact Test to assess whether there were more participants with erythema score > 1 in the silver fluoride group *vs*. the control group at 24 hrs and 7 days post-treatment. The primary end-point was assessed at 24 hrs. A *t* test assessed any differences in Gingival Index. Any white changes, ulceration, and staining (argyria) were reported.

Power Analysis

The data from the two sites were analyzed separately, and power is described below for the separate site analyses.

Reduction in tooth sensitivity—The primary end-point was assessed at 7 days post-treatment. In a similar desensiti- zation study comparing fluoride varnishes (Ritter *et al*., 2006), pain in response to air dropped from 36.9 (SD = 26.2) at baseline to 20.8 (SD = 4.3) at 2 wks post-treatment. We expected a similar or larger drop after 7 days with diammine silver fluoride, based on unpublished work from the University of Hong Kong, and little or no drop from the water. Thus, having 31 individuals in a group will allow for detection of effect size from 0.64 upwards, with an alpha of 0.05 and power of 0.8.

RESULTS

Participants

One hundred twenty-six adults (71 in Lima and 55 in Cusco) participated. About 378 candidates were screened between January and June 2010. The main reason (95%) for exclusion was lack of tooth sensitivity. The remainder were excluded because of the use of medications. No individuals were excluded because of tobacco use or coca. All of those eligible agreed to participate, but 10 were excluded because they failed to appear for the first visit. The proportion of women enrolled was 86% in Lima and 80% in Cusco. The average age of participants was 44 yrs and 43 yrs, respectively. There were no dropouts.

Participants and clinicians were blind to treatment assignment. Odor was not a threat to blinding, because the smell is not detectable clinically when such small quantities are used. Taste was not a threat in this study, because only minute amounts of material were applied and the tooth was air-dried after application.

Table 2. Numbers and Percentages of Participants with Erythema Score of 2 by Study Site and Condition

Study Site	Time	Condition		
Lima		Silver Fluoride (N = 37)	Control (N = 34)	
		n (%)	n (%)	*P*-value*
	Baseline	3 (8.1)	2 (5.9)	1.0
	24 hrs	3 (8.1)	2 (5.9)	1.0
	7 days	3 (8.1)	1 (2.9)	0.61
Cusco		Silver Fluoride (N = 26)	Control (N = 29)	
		n (%)	n (%)	*P*-value*
	Baseline	6 (23.1)	7 (24.1)	1.0
	24 hrs	10 (38.5)	2 (6.9)	0.0076
	7 days	3 (11.5)	3 (10.3)	1.0
Sites combined		Silver Fluoride (N = 63)	Control (N = 63)	
		n (%)	n (%)	*P*-value*
	Baseline	9 (14.3)	9 (14.3)	1.0
	24 hrs	13 (20.6)	4 (6.3)	0.035
	7 days	6 (9.5)	4 (6.3)	0.74

*Fisher's exact test

Clinical Effectiveness

The average pain scores before and after treatment, by site, are given in Table 1. At the Lima site, the silver fluoride group had slightly higher baseline scores (average = 57.3) than the control (average = 49.3; $P = 0.16$). At the Cusco site, the baseline scores were similar between the silver fluoride group (average = 51.7) and control (average = 51.6; $P = 0.98$). The primary study end-point was the change from baseline to 7 days. In Lima, the average change in pain score between baseline and day 7 for the silver fluoride group was -35.8 (SD = 27.7) mm *vs*. 0.4 (SD = 16.2) for the controls ($P < 0.0001$). In Cusco, the averagechange in pain score between baseline and day 7 for the silver fluoride group was -23.4 (SD = 21.0) mm *vs*. -5.5 (SD = 18.1) mm ($P = 0.0015$) for water.

Comparison of tooth sensitivity at 24 hrs and 7 days between study groups by analysis covariance, adjusted for the baseline sensitivity level, gave similar results.

There was no significant three-way interaction among study site, time, and study group (GEE linear regression; $P = 0.20$), but all two-way interactions were significant: study site by time($P = 0.043$), study site by study group ($P = 0.0006$), and study group by time ($P = 0.0076$). Hence, an analysis of time effect was done separately by study site. In Lima, there was no sig- nificant time-by-study-group interaction ($P = 0.21$). The overallstudy group difference in tooth sensitivity (over both time-points), adjusted for baseline sensitivity, was 29.9 ($P < 0.001$). The overall difference in sensitivity between 24 hrs and 7 days was 4.5 ($P = 0.014$). In Cusco, there was a significant study- group-by-time interaction ($P = 0.015$), so the overall studygroup difference is not reported. The differences in sensitivity between 24 hrs and 7 days were 16.9 ($P = 0.005$) for silver fluo-ride and 4.5 ($P = 0.097$) in the control group, respectively.

Safety

The number and percent of participants with a erythema score of 2 for the gingival tissue of the tooth treated for each treatment condition by site and time are given in Table 2. Scores were low; no individual had score 3, severe erythema, either before or after the application of silver fluoride. There was no difference in the proportion of participants with erythema score > 1 between the silver fluoride group and the placebo (Fisher's Exact Test, $P = 1.0$) at any time-point in the Lima population. There was a small but significant increase in the proportion of participants at the Cusco site who experienced an erythema score > 1 at 24 hrs ($P = 0.0076$). There was no difference in the proportion of participants with an erythema score > 1 between the groups in Cusco after 7 days ($P = 1.0$). No white or dark changes were noted in gingiva in any participant at any time in any condition at either site. An independent examiner, who was blind to treatment condition and time, examined the photographs and confirmed this lack of change.

The Gingival Index scores for each treatment condition and site are listed in Table 3. The mean (SD) Gingival Index scores for the mouth for treatment and control groups at base- line were: (Lima) silver fluoride, 0.29 (0.24), control 0.33 (0.35) ($P = 0.59$); and (Cusco) silver fluoride, 0.47 (0.24), control 0.38 (0.27) ($P = 0.19$). At 7 days, the mean (SD) changes in GI scores were: (Lima) silver fluoride, -0.02 (0.09), control 0.03 (0.13) ($P = 0.076$); and (Cusco) silver fluoride, -0.16 (0.27), control -0.03 (0.09) ($P = 0.023$). Similar results were observed after 24 hrs.

Photographs of the teeth suggest that the silver fluoride did not stain most exposed root surfaces (see Fig. 2 for an example). This result was found only when surfaces had untreated decay.

Table 3. Overall Gingival Index Score by Study Site and Condition

Study Site	Time	Condition		
Lima		Silver Fluoride (N = 37)	Control (N = 34)	
		Mean (SD) [Range]	Mean (SD) [Range]	*P*-value*
	Baseline	0.29 (0.24) [0.0, 1.2]	0.33 (0.35) [0.0, 1.5]	0.59
	24 hrs	0.28 (0.24) [0.0, 1.2]	0.35 (0.36) [0.0, 1.7]	
	Change from baseline	-0.01 (0.05) [-0.2, 0.1]	0.02 (0.07) [-0.2, 0.2]	0.076
	7 days	0.27 (0.23) [0.0, 1.2]	0.36 (0.39) [0.1, 1.8]	
	Change from baseline	-0.02 (0.09) [0.2, 0]	0.03 (0.13) [-0.5, 0.3]	0.076
Cusco		Silver Fluoride (N = 26)	Control (N = 29)	
		Mean (SD) [Range]	Mean (SD) [Range]	*P*-value*
	Baseline	0.47 (0.24) [0.1, 0.9]	0.38 (0.27) [0.0, 1.2]	0.19
	24 hrs	0.36 (0.21) [0.1, 0.8]	0.36 (0.24) [0.0, 1.2]	
	Change from baseline	-0.11 (0.16) [-0.6, 0.1]	-0.02 (0.12) [-0.3, 0.3]	0.020
	7 days	0.31 (0.19) [0.0, 0.8]	0.35 (0.26) [0.1, 1.2]	
	Change from baseline	-0.16 (0.27) [-0.8, 0.7]	-0.03 (0.09) [-0.3, 0.2]	0.023
Sites Combined		Silver Fluoride (N = 63)	Control (N = 63)	
		Mean (SD) [Range]	Mean (SD) [Range]	*P*-value**
	Baseline	0.36 (0.26) [0.0, 1.2]	0.35 (0.32) [0.0, 1.5]	0.72
	24 hrs	0.31 (0.23) [0.0, 1.2]	0.35 (0.31) [0.0, 1.7]	
	Change from baseline	-0.05 (0.12) [-0.6, 0.1]	0.00 (0.10) [-0.3, 0.3]	0.0023
	7 days	0.28 (0.22) [0.0, 1.2]	0.35 (0.33) [0.1, 1.8]	
	Change from baseline	-0.08 (0.20) [-0.8, 0.7]	0.00 (0.12) [-0.5, 0.3]	0.0028

*Two-sample test (unequal variances).
**Analysis of covariance, adjusted for study site, with heteroscedasticity-consistent standard errors.

DISCUSSION

In a population with teeth sensitive to air, this trial demonstrated that a topical solution of diammine silver fluoride was more effective than a placebo in reducing tooth pain. Reductions grew larger between 24 hrs and 7 days post-treatment. The study was conducted in two sites by different investigators to increase generalizability and had sufficient statistical power to detect clinically meaningful differences in pain. The study involved many more individuals than the typical study (Ritter *et al*., 2006).

Figure 2. Root caries at baseline (**left panel**), 24 hrs after treatment (**middle panel**), and 7 daysafter treatment with diammine silver fluoride (**right panel**).

The results, however, are consistent with those from similar studies of other desensitizers, such as self-administered 0.717% fluoride solution (Thrash *et al*., 1992) or fluoride varnish (Ritter *et al*., 2006). In the fluoride solution study, the authors concluded that two one-minute applications reduced sensitivity to cold. Participants in the varnish study experienced a pain reduction in response to ice, but not to air, at 2 wks. The current study reported significant pain reductions in response to air in 24 hrs that were maintained at 7 days. The magnitude of reduction was considerably greater than in the other studies. The current study did not use ice as a stimulus.

There were no unintended effects on the gingiva, and any inflammation resulting from the treatment was minor and transient. No staining of the gingival tissues was observed. Staining of teeth was found only when surfaces had untreated decay. The staining of carious dentin can be minimized bythe application of potassium iodide solution after treatmentwithout reducing the effect (Knight *et al*., 2006).

Diammine silver fluoride has been shown to arrest caries in animal models (Tanzer *et al*., 2010) and to be more effective than sodium fluoride varnish in human trials (Chu *et al*., 2002; Llodra *et al*., 2005; Rosenblatt *et al*., 2009; Tan *et al*., 2010).It did not cause abscesses in teeth with open cavities that were treated. The mechanism of action for caries arrest may be antimicrobial (Knight *et al*., 2009). Studies have also shown that diammine silver fluoride is free of adverse effects (Chu *et al*., 2002; Llodra *et al*., 2005; Tan *et al*., 2010). This suggests that diammine fluoride may be particularly effective in individuals in whom sensitivity is associated with demineralization and caries.

Diammine silver fluoride has been demonstrated to be a clinically effective and safe tooth desensitizer after 24 hrs and 7 days. Clinical trials are warranted to examine effectiveness over a longer period of time and in comparison with other agents.

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Original Contributions

Systematic Review

Controlling caries in exposed root surfaces with silver diamine fluoride

A systematic review with meta-analysis

Supplemental material is available online.

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ABSTRACT

Background. In this systematic review, the authors aim to assess the effect of silver diamine fluoride (SDF) in preventing and arresting caries in exposed root surfaces of adults.

Types of Studies Reviewed. Two reviewers independently searched for controlled clinical trials with at least 12 months of follow-up, without language or date of publication restraints, in 8 electronic databases, 5 registries of ongoing trials, and reference lists of narrative reviews.

Results. The authors found 2,356 unique records and included 3 trials in which the investigators randomly assigned 895 older adults. Investigators in all studies compared SDF with placebo; investigators in 1 also compared 38% SDF with chlorhexidine and sodium fluoride varnishes. The primary effect measures were the weighted mean differences (WMDs) in decayed or filled root surfaces (DFRS) and the mean differences in arrested carious lesions between SDF and control groups. The studies had low risk of bias in most domains. SDF applications had a significantly better preventive effect in comparison with placebo (WMD DFRS: 24 months, -0.56; 95% confidence interval, 0.77 to 0.36; 30 months or more, 0.80; 95% confidence interval, 1.19 to 0.42), and they were as effective as either chlorhexidine or sodium fluoride varnish in preventing new root carious lesions. SDF also provided a significantly higher caries arrest effect than did placebo (pooled results not calculated). Complaints about black staining of the carious lesions by SDF were rare among older adults.

Conclusions and Practical Implications. Yearly 38% SDF applications to exposed root surfaces of older adults are a simple, inexpensive, and effective way of preventing caries initiation and progression.

Key Words. Root caries; preventive dentistry; cariostatic agents; fluoride; dental health care for aged; systematic review.

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The cumulative incidence of root caries in people 60 years or older ranges from 12% to 77%; relevant risk factors are age, poor oral health, and periodontal disease.[1] The widespread occurrence of root caries in older adults translates into a peak of untreated caries in the world adult population at approximately 70 years of age.[2] Besides placing a huge financial burden on society,[2] untreated caries negatively affects the quality of life for older adults, especially because of pain, which can lead to psychological and physical discomfort, social disability, and even handicap.[3]

The development of root caries is a result of repeated cycles of demineralization and remineralization coupled with the degradation of the organic matrix of dentin and cementum. Demineralization initiates the caries process, but protein degradation plays a key role in its progression. Thus, topical applications of substances containing protease inhibitors could be an effective means of controlling root caries.[4]

Silver diamine fluoride (SDF) is an alkaline topical solution containing fluoride and silver that clinicians mainly have used for caries treatment in young children.[5] Besides reducing the growth of cariogenic bacteria and promoting the remineralization of the inorganic content of enamel and dentin, SDF prevents collagen degradation in dentin by inhibiting the activity of collagenases and cysteine cathepsins.[6] SDF is also known for its ability to desensitize hypersensitive teeth.[5]

Clinicians have used SDF for decades in some countries such as Australia, Brazil, China, and Japan.[5] The Food and Drug Administration of the United States approved it in 2016 as a dentin desensitizing agent, but clinicians also use it off-label for caries treatment.[7] The application of SDF is simple, painless, noninvasive, and inexpensive.[8,9] Therefore, it may be an attractive approach for the prevention and treatment of caries in older adults, especially in those with limited locomotion and impaired self-care ability.

Investigators in previous reviews on the effects of SDF in preventing and arresting root caries in adults conducted systematic searches of the evidence, but they lacked methodological sophistication.[10,11] They did not follow the guidelines for conducting and reporting systematic reviews,[12,13] and only the investigators in the 2017 review[11] provided some critical appraisal of the design and reporting of the included studies. Most investigators did not conduct meta-analysesdthat is, they did not combine the results of individual studies statistically to provide a more precise estimate of the degree to which SDF prevents new root carious lesions from occurring or arrests the progressionof existing lesions. Moreover, to our knowledge, investigators have not published reviews of head-to-head comparisons between SDF and other interventions (for example, sodium fluoride varnish [FV] or chlorhexidine [CHX] varnish). Our objective in this systematic review was to perform a qualitative and quantitative synthesis of the scientific evidence on the effect of SDF for preventing and arresting caries on exposed root surfaces of adults.

METHODS

This is a systematic review of randomized controlled clinical trials. We registered it at PROSPERO (CRD42016036963) and reported it according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[13] To be eligible for inclusion in our review, studies had to meet the following criteria:

- *participants*: adults of any age with exposed root surfaces at the beginning of the study;
- *intervention*: topical SDF solution (any concentration or frequency) applied by any health care worker in any setting;
- *comparisons*: no intervention, placebo, or any cariostatic agent or dental restorative material;
- *outcomes*: primary outcomes were the development of new carious lesions and the arrest of existing carious lesions in exposed root surfaces of permanent teeth within at least 12 months after product application (for example, 12, 24, or 30 months or more of follow-up). The sec-ondary outcome measures were any self-reported, caregiver-reported, or professionally diagnosed adverse events.

We developed a highly sensitive search strategy for MEDLINE and later adapted it for other databases and online repositories of trials with the help of a librarian (Appendix, available online at the end of this article). We searched the databasesdCochrane Central Register of Controlled Trials, Embase, MEDLINE via PubMed, Scopus, Web of Science, Latin American and Caribbean Health Sciences Literature, Biblioteca Brasileira de Odontologia, SciELOdin April 2016 without language or date of publication restrictions. We also searched 5 registries of ongoing trialsdClinicalTrials.gov, Brazilian Clinical Trials Registry, European Union Clinical Trials Register, International Standard Randomised Controlled Trial Number Registry and Current Controlled Trials, and Australian New Zealand Clinical Trials Registrydand the Brazilian database of theses and dissertations. We updated all searches in July 2017. We used cross-referencing from narrative reviews on the subject of SDF for caries prevention or arrest to identify additional articles.

We organized the records downloaded from each database into 1 core database (EndNote X7, Thomson Reuters). After training, 2 authors (B.O., A.R.) independently examined the titles and abstracts of all records that remained after removal of duplicates and decided which articles should be read in full. When a study apparently met the inclusion criteria but no abstract was available or there was not enough information in the title or abstract, we obtained and read the article. We examined studies in Japanese and Chinese regarding inclusion with the help of people knowledgeable in those languages.

We prepared and pilot tested an extraction data form. Two review authors (B.O., A.R.) independently read all the studies selected for inclusion and extracted the data. They also independently assessed the risk of bias for all included trials by using the Cochrane Risk of Bias Tool.[12] We

ABBREVIATION KEY

CHX: Chlorhexidine.
DFRS: Decayed or filled root surfaces.
FV: Sodium fluoride varnish.
KI: Potassium iodide.
N_f: No. of participants in analysis of caries incidence or arrest.
N_i: No. of participants randomly assigned.
OHE: Oral health education.
OHI: Oral hygiene instruction.
PF: Prevented fraction.
SDF: Silver diamine fluoride.

resolved disagreements between the reviewers about the inclusion of studies and the risk of bias in particular studies with the involvement of a third researcher (R.N.). We contacted study authors to obtain missing or unclear information.

For caries prevention, the primary outcome measure of treatment effect was the difference in mean caries increment (that is, follow-up mean number of decayed or filled root surfaces [DFRS] minus baseline mean number of DFRS) between the SDF and control groups (that is, water, tonic water, or another active treatment). We also calculated prevented fractions (PFs), which is themean caries increment in control groups minus mean caries increment in intervention groups divided by mean caries increment in control groups, for the comparison between SDF and placebo. We estimated confidence intervals (CIs) of PFs by using the Fieller method.[14] For caries arrest, the primary outcome measure of treatment effect was the difference in mean number of arrested lesions (that is, mean number of active root lesions at baseline that became arrested at follow-up) between the SDF and control groups.

Because the estimate of between-study variance under the random-effects model has poor precision when the number of studies is small,[15] we used the fixed-effects model to obtain pooled estimates of caries increment as weighted mean differences (WMDs) or PFs when combining the studies. We assessed study heterogeneity by using the c^2 test for heterogeneity and the Higgins index (I^2). We grouped the studies in our meta-analyses according to the duration of their follow- up: 12, 24, or 30 months or more. We could not pool the difference in caries increments regarding the comparisons between SDF and other active treatments (that is, CHX varnish and FV) because there was only 1 study for each comparison. When there was more than 1 SDF intervention group per study,[16,17] we combined them into a single group. We performed all analyses by using software(Stata 14, StataCorp) and followed the procedures described in the *Cochrane Handbook for Sys- tematic Reviews of Interventions*.[12]

RESULTS

The searches yielded 2,356 unique records; we assessed 22 publications for eligibility. Eventually, we included 4 articles from 3 trials[16-19] in which the investigators randomly assigned 895 older adults and analyzed data for 544, 712, and 460 participants at 12, 24, and 30 or more months of follow-up, respectively (Figure 1 and Table 1).[16-18] These participants had similar mean age (72.1-78.8 years) and low caries experience (that is, mean number of decayed and filled root surfaces at baseline ranging from 1.1-2.1) and consumed fluoridated water (0.5 parts per million). In all studies, both the test and control groups received individualized oral hygiene instruction. Investigators conductedall included trials in Hong Kong, used SDF at a 38% concentration, and compared it with a placebo(that is, water[17,18] or tonic water[16]). Two trials had 2 intervention groups: investigators in 1 trial[17] compared yearly SDF applications with or without participation in a biannual oral health education (OHE) program with a placebo, and investigators in another trial[16] compared yearly SDF applications followed or not by a potassium iodide (KI) application with a placebo. Investigators in 1 trial[18] also compared yearly SDF applications with quarterly applications of 1% CHX varnish and 5% FV (Table 1).[16-18] Investigators in 3 studies[16-18] provided data about caries prevention, and investigators in 2 studies[17,19] provided data about caries arrest. Investigators recorded active root caries when a sickle-shaped probe[18] or a Community Periodontal Index probe[17,19] could penetrate a lesion easily when applied with a light force. Investigators recorded inactive caries when they detected no soft dentin[17,19] and the root surface was smooth and dark brown or black.[17]

The investigators soundly designed, conducted, and reported the 3 trials. One trial[17] had all domains, except for allocation concealment, with low risk of bias. The other 2 trials[16,18] had 6 domains with low risk of bias and 2 domains with unclear risk of bias (Figure 2).[16-18]

Caries prevention

Results of the meta-analysis of the 3 studies with 24 months of follow-up and comparison of SDF with placebo showed that SDF applications significantly decreased the number of new root carious lesions (WMD DFRS, 0.56; 95% CI, 0.77 to 0.36) (Figure 3).[16-18] The PF for root caries prevention ranged from 50.30% to 68.35%, depending on follow-up duration (Figure 4).[16-18] When investigators compared SDF with SDF followed by KI, they observed no significant difference in caries increment after 30 months of follow-up.[16] Because in the study by Zhang and colleagues[17] only the test group that received a co-intervention (OHE) had a significantly lower new caries

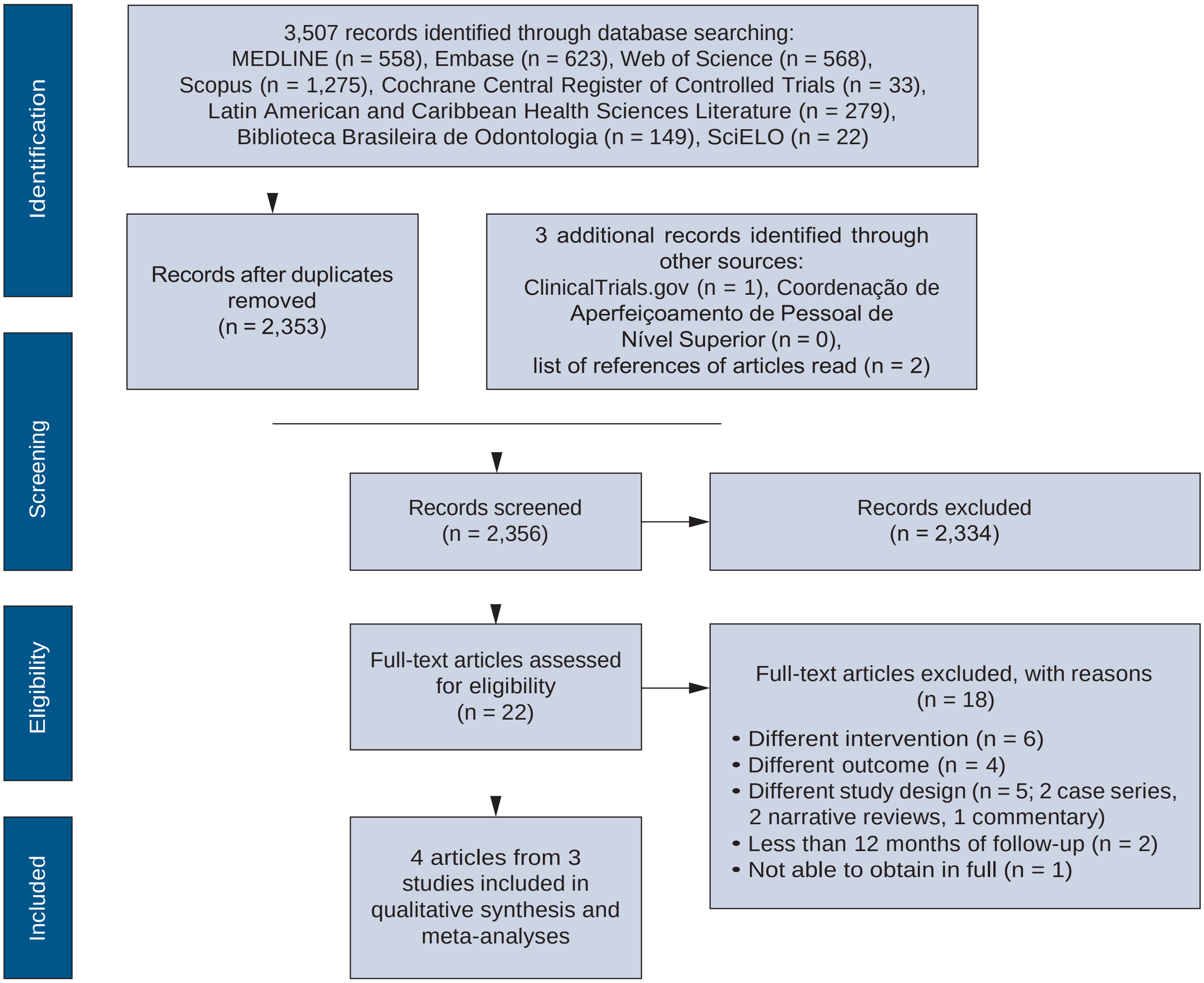

Figure 1. Flow diagram showing the process of identifying, screening, assessing for eligibility, and excluding and including studies.

increment in comparison with the placebo group, we performed a sensitivity analysis excluding this group from the comparison between SDF and placebo. The pooled WMD and PF changed from 0.56 to 0.54 (95% CI, 0.75 to 0.33) and from 50.30% to 52.05% (95% CI, 38.55 to 65.55), respectively.

We based the comparisons between SDF and FV or CHX varnish on 1 study.[18] CHX had a significantly higher preventive effect than did SDF at 12 months of follow-up, but there were no significant differences between SDF and FV at any of the follow-up periods analyzed (that is, 12, 24, or 36 months) or between SDF and CHX varnish at 24 months of follow-up or more (Figure 5).

Caries arrest

We observed significantly higher mean numbers of arrested lesions in the test groups than in the placebo group after 24 months of follow-up in 1 study.[17] In the other study,[16] the investigators provided the results as a percentage of caries arrest, and the test groups had significantly higher percentages of carious lesions arrested than did the placebo group at 12, 24, and 30 months of follow-up. In this study, the investigators randomly assigned 323 participants to the test and controlgroups, but only 83 subjects were included and 67 were analyzed in the authors' reporting on cariesarrest (Table 2).[16,17]

Investigators in 2 studies[16,18] reported that the interventions were well accepted by the older adult participants. In 1 trial, 3.5% of all participants complained about the black staining of their

Table 1. Characteristics of the included studies.

STUDY, COUNTRY	TOTAL FOLLOW-UP DURATION (MONTHS)	N_i* AND N_f†	MEAN (STANDARD DEVIATION) AGE OF PARTICIPANTS (YEARS) AND CARIES EXPERIENCE (MEAN NO. OF DFRS‡) AT BASELINE	INTERVENTION	COMPARISON
Tan and Colleagues,[18] 2010, China	36	N_i ¼ 306 2 mo), 227 (24 mo) and 203 (36 mo)	Age ¼ 78.8 (6.2) DFRS ¼ 2.1	OHI§ and 38% SDF{ applications (every 12 mo) or OHI and CHX# varnish (every 3 mo) or OHI and FV** (every 3 mo) onto all exposed root surfaces	OHI and water applications (every 12 mo) onto all exposed root surfaces
Zhang and Colleagues,[17] 2013, China	24	N_i ¼ 266 N_f ¼ 227	Age ¼ 72.5 (5.7) DFRS ¼ 1.9	OHI and 38% SDF applications (every 12 mo) or OHI and 38% SDF applications (every 12 mo) and OHE†† program (every 6 mo) onto all exposed root surfaces	OHI and water applications (every 12 mo) onto all exposed root surfaces
Li and Colleagues,[16] 2017, China	30	N_i ¼ 323 N_f ¼ 297 (12 mo), 258 (24 mo), and 257 (30 mo)	Age ¼ 72.1 (6.3) DFRS ¼ 1.1	OHI and 38% SDF applications or OHI and 38% SDF applications and KI‡‡ applications (every 12 mo) onto all exposed root surfaces	OHI and tonic water applications (every 12 mo) onto all exposed root surfaces

* N_i: No. of participants randomly assigned. † N_f: No. of participants in analysis of caries incidence. ‡ DFRS: Decayed or filled root surfaces. § OHI: Oral hygiene instruction. { SDF: Silver diamine fluoride. # CHX: Chlorhexidine. ** FV: Sodium fluoride varnish. †† OHE: Oral health education. ‡‡ KI: Potassium iodide.

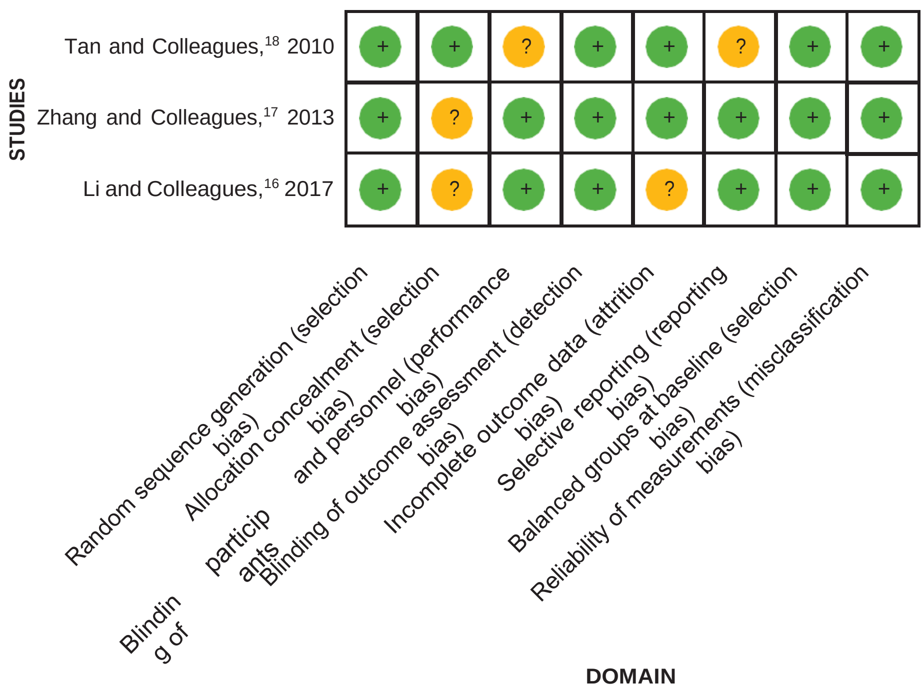

Figure 2. Ascertainment of the risk of bias in the included studies. Green indicates low risk, and yellow indicates unclear risk.

treated root surfaces.[16] In another, only 2 older adult participants, both in the SDF group, raised the same complaint (additional information provided by 1 of the authors).[18]

DISCUSSION

Our findings show that annual applications of 38% SDF in older adults decreased the incidence of new carious lesions in exposed root surfaces by at least 50%; the longer the duration of the intervention, the greater the effect. Limited evidence with low risk of bias indicated that SDF was significantly more effective in preventing the development of new carious lesions compared with placebo and was similar to or better than FV and CHX varnish.

Study	WMD (95% CI)	Percentage Weight
12 months		
Tan and Colleagues,[18] 2010	–1.10 (–1.54 to –0.66)	23.01
Li and Colleagues,[16] 2017	–0.30 (–0.54 to –0.06)	76.99
Subtotal I^2 = 89.9%, P = .002	–0.48 (–0.69 to –0.27)	100.00
24 months		
Tan and Colleagues,[18] 2010	–1.30 (–2.01 to –0.59)	8.52
Zhang and Colleagues,[17] 2013	–0.47 (–0.96 to 0.02)	17.55
Li and Colleagues,[16] 2017	–0.50 (–0.74 to –0.26)	73.93
Subtotal I^2 = 56.4%, P = .101	–0.56 (–0.77 to –0.36)	100.00
30 months or more		
Tan and Colleagues,[18] 2010	–1.80 (–2.86 to –0.74)	13.43
Li and Colleagues,[16] 2017	–0.65 (–1.07 to –0.23)	86.57
Subtotal I^2 = 74.6%, P = .047	–0.80 (–1.19 to –0.42)	100.00

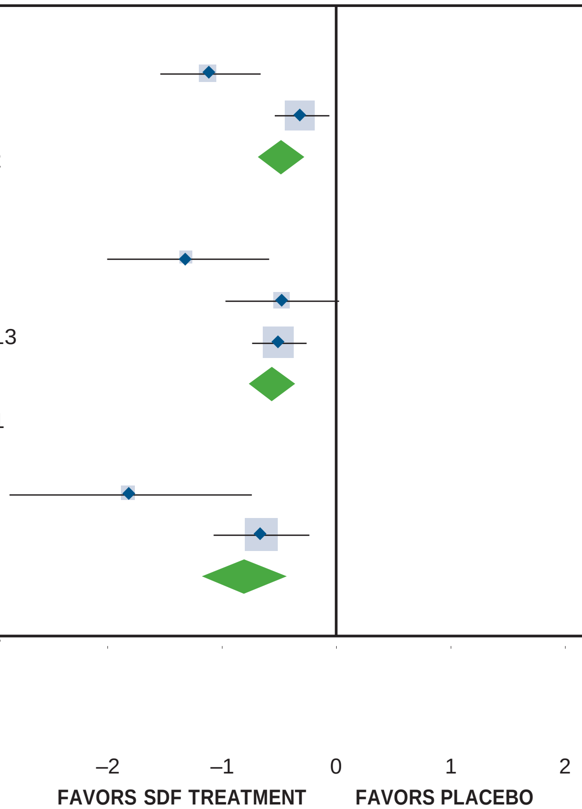

Figure 3. Comparisons of the mean increment in the number of decayed or filled root surfaces of permanent teeth in the silver diamine fluoride (SDF) and placebo groups according to duration of follow-up (12, 24, or 30 months or more). CI: Confidence interval. WMD: Weighted mean difference.

Study	PF (95% CI)	Percentage Weight
12 months		
Tan and Colleagues,[18] 2010	71.38 (55.91 to 86.84)	83.75
Li and Colleagues,[16] 2017	52.74 (17.62 to 87.85)	16.25
Subtotal I^2 = 0.0%, P = .341	68.35 (54.20 to 82.51)	100.00
24 months		
Tan and Colleagues,[18] 2010	61.69 (38.29 to 85.08)	30.14
Zhang and Colleagues,[17] 2013	28.49 (1.32 to 55.66)	22.35
Li and Colleagues,[16] 2017	53.34 (34.71 to 71.98)	47.51
Subtotal I^2 = 42.7%, P = .175	50.30 (37.46 to 63.15)	100.00
30 months or more		
Tan and Colleagues,[18] 2010	66.92 (45.50 to 88.33)	49.92
Li and Colleagues,[16] 2017	53.14 (31.76 to 74.52)	50.08
Subtotal I^2 = 0.0%, P = .372	60.02 (44.89 to 75.15)	100.00

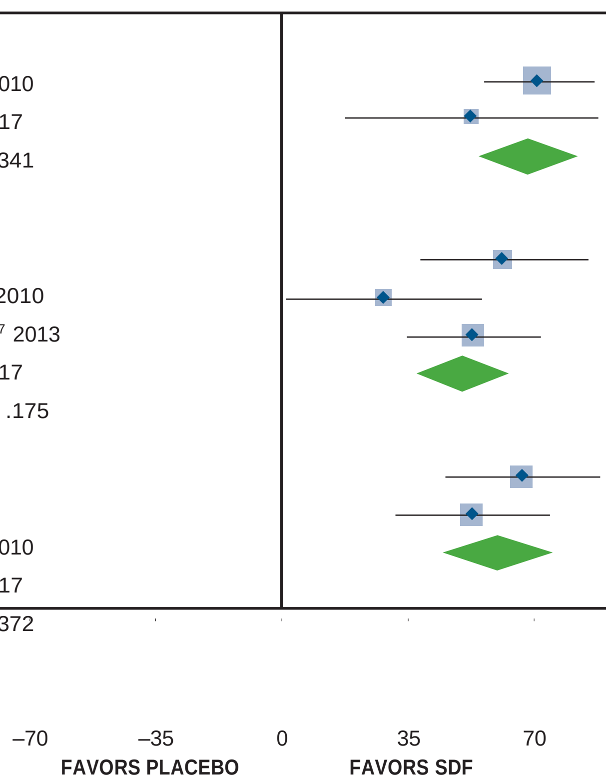

Figure 4. Comparisons of the prevented fractions (PFs) in root surfaces of permanent teeth in the silver diamine fluoride (SDF) and placebo groups according to duration of follow-up (12, 24, or 30 months or more). CI: Confidence interval.

In our meta-analyses for caries prevention, we combined 2 SDF test groups into 1 SDF group in 2 of the included trials. Investigators in 1 trial[17] tested whether the benefits of SDF applications would be increased by participation in a biannual OHE program that trained dental hygienists conducted and that emphasized the prevention of snacking habits, correct toothbrushing practices, and

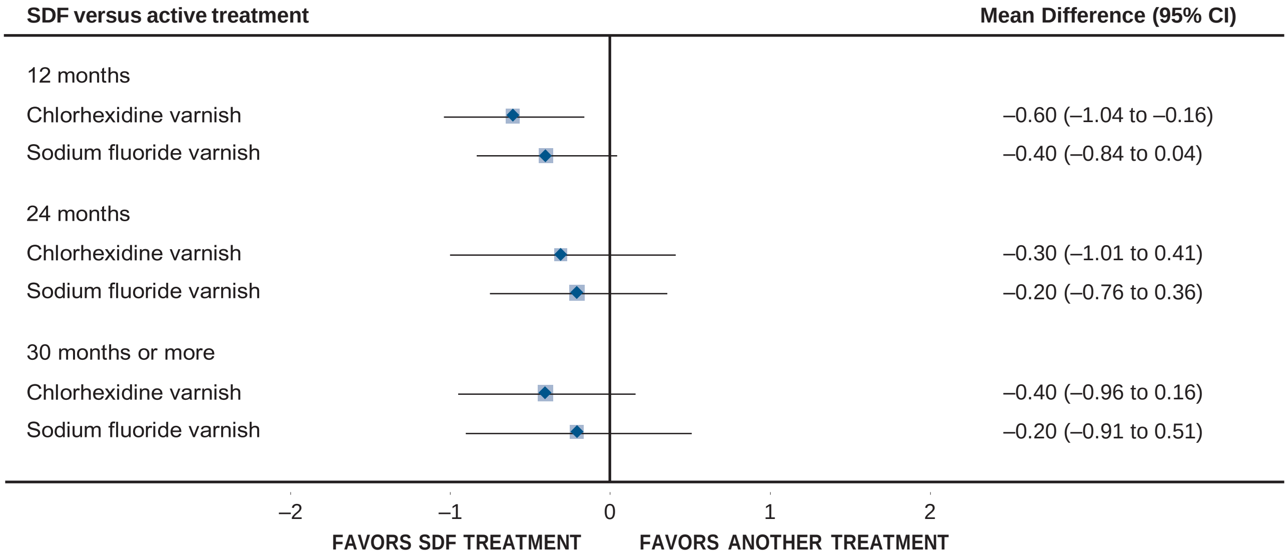

Figure 5. Comparisons of the mean increment in the number of decayed or filled root surfaces of permanent teeth in the silver diamine fluoride (SDF) and active treatment groups according to duration of follow-up (12, 24, or 30 months or more). CI: Confidence interval. WMD: Weighted mean difference.

Table 2. Results of the individual studies regarding caries arrest by duration of follow-up.

STUDY	OUTCOME	N_i* AND N_f† ACCORDING TO FOLLOW-UP DURATION	RESULTS IN INTERVENTION GROUP	RESULTS IN COMPARISON GROUP
Zhang and Colleagues,[17] 2013	Mean (Standard Deviation) No. of Arrested Root Caries Surfaces	N_i ¼ 266 (24 mo) N_f ¼ 227	OHI[‡] and SDF[§] (n ¼ 83) ¼ 0.28 (0.02) OHI and SDF and OHE[¶] (n ¼ 69) ¼ 0.33 (0.10)	OHI and water (n ¼ 75) ¼ 0.04 (0.02)
Li and Colleagues,[16] 2017	Percentage of Arrested Root Caries Surfaces	N_i ¼ 323; 83 with active root caries		
		N_f ¼ 75 (12 mo)	OHI and SDF (n ¼ 27) ¼ 61.0% OHI and SDF and KI[#] (n ¼ 29) ¼ 75.9%	OHI and tonic water (n ¼ 19) ¼ 32.1%
		N_f ¼ 65 (24 mo)	OHI and SDF (n ¼ 26) ¼ 82.1% OHI and SDF and KI (n ¼ 23) ¼ 85.4%	OHI and tonic water (n ¼ 16) ¼ 28.6%
		N_f ¼ 67 (30 mo)	OHI and SDF (n ¼ 27) ¼ 90.0% OHI and SDF and KI (n ¼ 24) ¼ 92.5%	OHI and tonic water (n ¼ 16) ¼ 45.0%

* N_i: No. of participants randomly assigned. † N_f: No. of participants in analysis of caries incidence. ‡ OHI: Oral hygiene instruction. § SDF: Silver diamine fluoride. ¶ OHE: Oral health education. # KI: Potassium iodide.

adoption of additional tooth cleaning aids. This program was costly and time consuming, but only the SDF plus OHE group had a significantly lower new caries increment in comparison with the placebo group. Considering that toothbrushing behavior improvement did not differ significantly between the SDF only and SDF plus OHE groups and that sugar snacking plays a major role in caries development, it is likely that an unmeasured modification of the participants' dietary habits might have contributed to the lower caries incidence in the SDF plus OHE group. However, results of a sensitivity analysis excluding the SDF plus OHE group from the comparison between SDF and placebo showed that the effect of this co-intervention on the pooled effect was negligible. The investigators in the other trial compared the use of SDF alone with the use of SDF plus KI solution.[16,19] The KI application immediately after the SDF application did not interfere with the SDF's effectiveness in preventing[16] root caries.

Despite reaching a conclusion similar to that of a meta-analysis in which the authors combined the results of 2 trials with different follow-up periods[20] regarding the efficacy of SDF for root caries prevention, we obtained a more conservative estimate of effect. Because we pooled the results of 3 trials in our meta-analyses, our estimate of effect is probably more precise. Moreover, because we grouped the studies in our meta-analyses according to follow-up duration, we were able to show that the preventive effect of SDF in root surfaces seems to increase with increasing duration of therapy.

To our knowledge, investigators have not shown this finding before, and it requires more thorough investigation.

When we compared SDF with other active treatments for root caries prevention, evidence from only 1 study indicated no difference between the yearly SDF and quarterly FV or CHX varnish applications, except for the comparison between SDF and CHX varnish at 12 months, which favored CHX. Authors of a 2015 meta-analysis estimated a reduction of 0.67 mean DFRS in participants treated with CHX varnish in comparison with those treated with placebo.[20] Taken together, these findings suggest that SDF and CHX varnish may have a similar effect on the pre- vention of root caries. Nevertheless, results of an analysis of cost-effectiveness in the context of theGerman health care system showed that quarterly applications of CHX varnish were not cost- effective, whereas SDF was more cost-effective than no treatment, especially in populations witha high risk of developing caries.[21] The lack of difference between the root caries preventive effect ofSDF and FV contrasts with what has been observed in primary teeth, where yearly 38% SDF ap- plications performed significantly better than did quarterly 5% sodium FV applications.[22] More well-designed clinical trials in which the investigators compare different frequencies and intervals between applications of SDF, CHX varnish, fluoride varnish, and other cariostatic agents are needed.

The assessment of the effect size of SDF on the arrest of root caries was hindered by the difference in outcome measures used in the studies, and we could not pool the results. However, there is good-quality evidence accrued from 1 trial[17] that annual 38% SDF applications effectively arrest root caries. Moreover, KI application immediately after SDF or participation in a biannual OHE program together with yearly SDF applications does not seem to interfere with SDF's caries-arresting effect.[19]

The esthetics of the arrested lesions was not a concern among the older adults who participated in the studies included in our review. However, adults of different cultural backgrounds or with a higher number of root caries surfaces or lesions in the anterior teeth may consider the darkening effect of SDF unacceptable.[23] Investigators in 1 trial tested whether the use of a KI solution immediately after SDF application would reduce the black staining produced by the silver ions present in SDF; however, the study's results failed to show a significant reduction of the black staining with use of the KI solution.[16,19] Thus, there is still a need to investigate whether this change in color in SDF-treated carious lesions can be minimized.

The results of this systematic review are limited by the low number of clinical trials in which the investigators addressed our research question and the lack of information from the included trials on the potential adverse effects of the intervention other than the darkening of carious lesions. In addition, all of the included trials were from the same group of investigators and enrolled Chinese older adult participants with a low risk of developing caries. The extent to which the findings can be generalized to other populations (for example, older adults with higher caries risk, not exposed to fluoridated water, not receiving individualized oral hygiene instruction regularly, or having different dietary habits) and reproduced by other investigators needs to be investigated further. In addition, we encountered moderate to considerable statistical heterogeneity when we pooled the WMDs. This finding is difficult to explain because relevant clinical and methodological variations among the studies are not apparent, and there are not enough studies to allow a reliable statisticalinvestigation of the reasons for heterogeneity. Some have suggested the change of the effect measure as an alternative to deal with heterogeneity.[12] When we estimated the pooled PF, we observed no heterogeneity, and results were consistent with those obtained through meta-analyses of WMDs, confirming the effectiveness of SDF for preventing root caries.

CONCLUSIONS

Yearly 38% SDF applications to exposed root surfaces of older adults are effective against caries initiation and progression. The preventive effect of SDF for root caries is similar to that of 5% FV and 1% CHX varnish. Further research is needed to replicate these findings and to determine the best frequency and interval of SDF applications. Given the potential of SDF for both prevention and arrest of caries, its low cost, and its simplicity of application, investigators in future studies in older adult populations should consider the effect of SDF on satisfaction with dental health care, quality of life, and the cost benefit of using SDF in lieu of more complex treatments at this stage oflife. n

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2018.03.028.

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APPENDIX

Search strategy for MEDLINE via PubMed

Search #1 ("silver diamine fluoride"[Supplementary Concept] OR "silver diamine fluoride"[All Fields]) OR ("silver fluoride"[Supplementary Concept] OR "silver fluoride"[All Fields]) OR ("silver nitrate"[MeSH Terms] OR ("silver"[All Fields] AND "nitrate"[All Fields]) OR "silver nitrate"[All Fields]) OR (("silver"[MeSH Terms] OR "silver"[All Fields]) AND ("nanoparticles"[MeSH Terms] OR "nanoparticles"[All Fields] OR "nanoparticle"[All Fields]))
Search #2 (((((tooth demineralization[MeSH Terms]) OR caries) OR dental decay) OR cavit*) OR tooth remineralization) OR tooth discoloration
#1 AND #2

JAMA Network Open

Original Investigation | Pediatrics

Effect of Silver Diamine Fluoride on Caries Arrest and Prevention
The CariedAway School-Based Randomized Clinical Trial

Ryan Richard Ruff, PhD; Tamarinda Barry-Godín, DDS; Richard Niederman, DMD

Abstract

IMPORTANCE Dental caries is the most common global childhood disease. To control caries, the Centers for Disease Control and Prevention recommends school-based caries prevention, and the World Health Organization lists glass ionomer cement and silver diamine fluoride as essential medicines for oral disease.

OBJECTIVE To determine the noninferiority of silver diamine fluoride with fluoride varnish vs traditional glass ionomer sealants with fluoride varnish after 2 years when provided to children via a school-based health care program.

DESIGN, SETTING, AND PARTICIPANTS The CariedAway study is an ongoing single-blind, cluster randomized, noninferiority trial conducted between February 1, 2019, and June 1, 2023, among 2998 children in 47 New York City primary schools. Children aged 5 to 13 years of any race and ethnicity were recruited from block-randomized schools. Inclusion criteria for schools were a student population of at least 50% Hispanic or Latino or Latina ethnicity and/or Black race and at least 80% of students receiving free or reduced-cost lunch. Statistical analysis is reported through March 2022.

INTERVENTIONS Children received a single application of silver diamine fluoride with fluoride varnish or an active comparator of glass ionomer sealants and atraumatic restorations with fluoride varnish.

MAIN OUTCOMES AND MEASURES Primary outcomes were caries arrest and incidence after a 2-year follow-up, assessed using mixed-effects multilevel models and clustered 2-sample proportion tests. The noninferiority margin was 10%. Intention-to-treat analysis was performed using multiple imputation.

RESULTS A total of 2998 children (1566 girls [52.2%]; mean [SD] age at baseline, 6.6 [1.2] years; 1397 Hispanic or Latino or Latina children [46.6%]; 874 [29.2%] with untreated dental caries) were recruited and treated from September 16, 2019, to March 12, 2020. Follow-up observations were completed for 1398 children from June 7, 2021, to March 2, 2022. The mean (SE) proportion of children with arrested caries was 0.56 (0.04) after experimental treatment and 0.46 (0.04) after control treatment (difference, −0.11; 95% CI, −0.22 to 0.01). The mean (SE) proportion of patients without new caries was 0.81 (0.02) after experimental treatment and 0.82 (0.02) after control treatment (difference, 0.01; 95% CI, −0.04 to 0.06). Analysis of imputed data for the full sample did not deviate from per-protocol analyses. There were no adverse events.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, silver diamine fluoride with fluoride varnish was noninferior to sealants and atraumatic restorations with fluoride varnish for caries arrest and prevention. Results may support the use of silver diamine fluoride as an arresting and preventive agent in school-based oral health programs.

(continued)

Key Points

Question Is silver diamine fluoride noninferior to dental sealants, the standard of care, for the arrest and prevention of caries in a school-based program?

Findings In this cluster randomized noninferiority trial, the proportion of children with arrested caries after 2 years was 0.56 among those receiving silver diamine fluoride and 0.46 among those receiving glass ionomer sealants. The proportion of children who remained free from caries was 0.81 among those receiving silver diamine fluoride and 0.82 among those receiving sealants.

Meaning This study found that silver diamine fluoride was noninferior to traditional sealants when used in a school-based program.

+ Visual Abstract

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03442309

JAMA Network Open. 2023;6(2):e2255458. doi:10.1001/jamanetworkopen.2022.55458

Introduction

Dental caries (tooth decay) is a natural process by which bacteria in the biofilm cause fluctuations in pH, leading to enamel erosion and a resulting visible lesion.[1] If left untreated, caries can result in pain, abscess, and systemic infection, leading to functional and/or psychosocial impairment.[2] Caries is the most prevalent childhood disease in the world and is most prominent among low-income populations.[3] The disproportionate burden of caries in vulnerable groups stems largely from lower use of dental services; those most at risk often lack access to preventive services or affordable dental care.[4,5]

To reduce children's caries burden, the Centers for Disease Control and Prevention recommends dental sealants and topical fluorides as part of a school-based caries prevention program.[6,7] Similarly, the World Health Organization lists silver diamine fluoride (SDF) and glass ionomer cement as essential medicines for dental caries.[8] The efficacy of these treatments is well established: clinical guidelines for topical fluoride conclude that a 2.3% concentration of fluoride varnish or 1.2% fluoride gel is recommend for children, adolescents, and adults[9]; fluoride varnish had a 70% reduction in demineralized white lesions compared with placebo[10]; dental sealants significantly reduce caries incidence and arrest the progression of noncavitated lesions, showing an 11% reduction in the proportion of carious surfaces when comparing sealants with no sealant[11]; atraumatic restorative treatment noninvasively arrests caries, with median survival times equivalent to those of more traditional restorative intervention[12-14]; and SDF reduces the risk of carious lesions and controls caries progression, including a relative risk of 0.6 in the arrest of carious lesions of root surfaces compared with fluoride varnish.[15,16]

Use of alternative medicaments in school-based caries prevention may obviate the financial and workforce barriers known to limit school sealant programs.[17] For example, SDF is cost effective,[18] can be applied in less time than dental sealants,[19] and can be provided by registered nurses. As a result, evidence that SDF is comparable in the treatment of dental caries in a school setting may substantially improve the reach and effectiveness of caries prevention as a dental public health intervention. We conducted the CariedAway school-based pragmatic (conducted in everyday settings)[20] randomized clinical trial to test the noninferiority of SDF plus fluoride varnish compared with traditional dental sealants and fluoride varnish. We report on the 2-year differences in caries arrest and caries incidence.

Methods

This study received ethical approval from the New York University School of Medicine institutional review board and is reported following the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline for randomized clinical trials. Parents provided written informed consent, and participants gave oral assent. Detailed study information has been previously published in an available trial protocol[21] and is included in Supplement 1.

A stakeholder and community advisory board was created to inform the design and conduct of the trial and assist in the interpretation and dissemination of findings. The board consisted of 35 local health and education leaders, including representatives from the New York City Department of Health, researchers, clinicians, school principals, school nurses, teachers, and parents.

Design and Participants

CariedAway is an ongoing cluster randomized, single-blind, pragmatic noninferiority clinical trial conducted in New York City primary schools between February 1, 2019, and June 1, 2023, to evaluate the effectiveness of SDF with fluoride varnish in comparison with an established, active comparator of glass ionomer sealants and atraumatic restorative treatment with fluoride varnish for dental caries. A total of 60 schools were originally proposed to be enrolled. The study used a 2-stage enrollment process. First, eligible schools in the New York City area were solicited for participation. Inclusion criteria for school enrollment included an overall student population of 80% or higher receiving free or reduced-cost lunch and at least 50% of enrolled students reporting Hispanic or Latino or Latina ethnicity and/or Black race. Second, informational letters and informed consent documents were distributed to all children enrolled in participating schools.

Exclusion criteria for individual participants included any child who did not speak English and children enrolled in special education classrooms. For ethical purposes, any child in an enrolled school was eligible to receive care. However, only children in grades kindergarten through grade 3 were included in the study for analysis because they were expected to remain enrolled in the school at the time of follow-up. Due to contractual obligations with the New York State Department of Health, data could only be collected from children if they were still enrolled in the included schools.

Randomization

Consenting schools were listed in ascending order of population size and block randomized in blocks of 4 schools using a 1:1 allocation ratio. Allocation sequences were created using a random number generator.[22] Allocation was performed at the school level and concealed from the potential participants within each school. Randomization was performed by R.R.R. and verified by T.B.-G.

Interventions and Procedures

Children were randomized at the school level to receive either an experimental condition or standard of care active comparator treatment. The experimental treatment consisted of 5% fluoride varnish applied to all teeth and 38% SDF (2.24 mg/dose of fluoride ion) applied to all asymptomatic cavitated lesions and brushed on all pits and fissures of bicuspids and molars. The standard of care treatment included identical application of fluoride varnish, glass ionomer sealants applied to all pits and fissures of bicuspids and molars, and placement of atraumatic restorations on all frank asymptomatic cavitated lesions.

Treatments were provided in a single application after a baseline examination. For the experimental treatment, a single drop of 38% SDF was dispensed into a disposable mixing well and applied as specified for a minimum of 30 seconds. Treated sites were then air dried for a minimum of 60 seconds. For standard of care, a cavity conditioner was applied to pits and fissures for 10 seconds. Glass ionomer sealant capsules were mixed for 10 seconds at 4000 revolutions per minute and then applied directly via the finger-sweep technique and digitally applied to all pits and fissures, ensuring that closed margins were achieved. All treatments were provided in a dedicated room in each school using mobile equipment by dental hygienists or registered nurses with the support of assistants and under the supervision of a licensed dentist. No personalization of the treatment plan was required or performed.

Outcomes

At each observation, standardized study clinicians performed full-mouth visual-tactile oral examinations. Teeth were assessed as being present or missing intraorally. Caries diagnosis was performed using the standard International Caries Detection and Assessment System (ICDAS II) adapted criteria for epidemiology and clinical research settings.[23] Individual tooth surfaces were assessed as being intact or sound (ICDAS II codes 0-4), sealed, restored, decayed (ICDAS II codes 5-6), or arrested.

Our primary outcomes were the proportion of children with arrested carious lesions (arrest) and the proportion of children with no cumulative incidence of decayed teeth from previously sound dentition (prevention). Arrest failure was recorded if the tooth presented at baseline with untreated caries, received treatment at baseline with either experimental treatment or standard of care, and presented at follow-up with either untreated caries or a filling (indicative of treatment for caries applied by an external clinician). If a tooth was exfoliated prior to the 2-year follow-up that was coded as arrested after baseline treatment, that tooth was discounted from analysis. Caries prevention compared the cumulative incidence of caries in each treatment group. Children with new caries included those who presented at follow-up with either (1) untreated carious lesions or (2) presence of a filling not present at baseline. The decay determination was previously used in assessing the effectiveness of the active comparator.[24,25]

Outcomes were aggregated at the individual level to mitigate within-individual correlation for participants having multiple lesions at baseline or multiple new caries at follow-up. If a child at baseline presented with multiple carious lesions that received treatment, a failure of any treated lesion at follow-up was considered person-level arrest failure regardless of the status of other lesions. Similarly, caries incidence was considered prevention failure regardless of how many lesions were observed.

Other outcomes of the CariedAway trial not reported here include the 4-year prevention rate of caries, the noninferiority of registered nurses vs dental hygienists in the effectiveness of treatment with SDF,[26] and effects on oral health-related quality of life,[27] academic performance, and school absenteeism.

Demographic Variables

Demographic data (including age, sex, and race and ethnicity) were self-reported by parents or guardians on informed consent documents. Selectable options for race and ethnicity were the same as those required by the New York City Department of Education, including American Indian or Alaskan Native, Asian, Black or African American, Hawaiian or Pacific Islander, and White. An "Other" option was provided that was to include any other race not listed. Ethnicity options included Hispanic (Latino or Latina) or non-Hispanic. Race and ethnicity data were collected to ensure that the targeted study population was included and for future stratified analyses.

Blinding

Participants were blinded to their group assignments; however, given the staining effect of SDF on untreated decay, it was possible that patients could derive their treatment assignment. Clinicians and examiners were not blinded due to the specific procedures required for each treatment.

Statistical Analysis

Statistical analysis is reported through March 2022. Our approach for noninferiority followed established guidelines.[28] Power analyses for primary clinical outcomes was calculated for a 2-group clustered trial design and previously reported (N = 396).[21] The intraclass correlation for dependence within cluster was estimated via mixed-effects multilevel logistic models.

Our noninferiority margin was predetermined to be 10% as the maximum clinically relevant difference and also agrees with the fixed margin method when comparing our active control with a placebo, in which prior investigations showed a prevalence of pit or fissure dentin caries of 1.6% vs 4.6% for dental sealants vs placebo and a risk reduction of 10% among children receiving sealants and atraumatic restorative treatment.[24,25] For analysis of the proportion of children with arrested caries or no caries incidence in active control (C) and SDF (S) treatments, our null hypothesis was thus H_0: $C - S \geq 10$, while our alternative hypothesis was H_a: $C - S < 10$, where 10 represents the selected noninferiority margin. Our statistical test for this hypothesis used 2-sample proportion tests, adjusting for any clustering effect of schools and comparing the upper bound of the 2-sided 95% CI for (*C* − *S*) with the noninferiority margin.[28,29] As a sensitivity analysis, we performed similar tests using bootstrapped 95% CIs with schools as the cluster unit and 10 000 replications.

Intention-to-treat analysis was performed using multiple imputation. Five imputed data sets were generated for the full follow-up sample (N = 2998). Imputed data sets were then separated for arrest and prevention outcomes, following primary analysis procedures, and analyzed using logistic regression. Analysis was conducted in Stata, version 17 (StataCorp LLC) and R, version 1.4 (R Group for Statistical Computing). All *P* values were from 1-sided tests and results were deemed statistically significant at $P < .025$.

Results

A total of 2998 children (1566 girls [52.2%] and 1432 boys [47.8%]; mean [SD] age at baseline, 6.6 [1.2] years) were recruited and treated. A total of 314 children (10.5%) presented at baseline with preexisting dental sealants on any tooth, and 874 (29.2%) had untreated dental caries (**Table 1**). Hispanic or Latino and Black children comprised 63.8% of the analytic sample (887 of 1390). The mean (SD) time that elapsed from baseline to follow-up for the analytic sample was 718 (87.2) days. The intraclass correlation coefficient was 0.034 for caries arrest and 0.0031 for caries prevention.

Our analytic sample consisted of all children in kindergarten through grade 3 who were enrolled, randomized, and treated and who completed a follow-up visit after approximately 2 years. A total of 4718 children across 47 schools were treated at baseline between September 16, 2019, and March 12, 2020, prior to suspension due to COVID-19 (**Figure 1**). As all children in schools were eligible for care, a subset of these participants were treated for ethical reasons but were outside of analytic grades, including children in grades 4 and 5 who would not be enrolled in school long enough to undergo follow-up. When restricted to children in viable grades, the enrolled and treated sample was 2998. We completed follow-up observations between June 7, 2021 and March 2, 2022, with 1398 children (611 in the experimental group, 20.4% of the enrolled and treated sample of 2998 children; 787 in the active control group, 26.3% of the enrolled and treated sample of 2998 children), for an overall follow-up rate of 29.6% (1398 of 4718) among all children enrolled and 46.6% (1398 of 2998) among all viable participants. As caries arrest can be evaluated only in children who had untreated decay at baseline, the analytic sample for arrest was 413 patients. The analytic sample for prevention was 985 patients. There were no adverse events reported.

Table 1. Baseline Sample Description Overall and by Treatment Group

Characteristic	Full sample, No. (%)			Follow-up sample, No. (%)		
	All (N = 2998)	Experimental group (n = 1554 [51.8%])	Control group (n = 1444 [48.2%])	All (N = 1398)	Experimental group (n = 611 [43.7%])	Control group (n = 787 [56.3%])
Girls	1566 (52.2)	786 (50.6)	780 (54.0)	753 (53.9)	321 (52.5)	432 (54.9)
Boys	1432 (47.8)	768 (49.4)	664 (46.0)	645 (46.1)	290 (47.5)	355 (45.1)
Race and ethnicity						
Asian	36 (1.2)	20 (1.3)	16 (1.1)	24 (1.7)	14 (2.3)	10 (1.3)
Black	456 (15.2)	249 (16.0)	207 (14.3)	208 (14.9)	98 (16.0)	110 (14.0)
Hispanic	1397 (46.6)	685 (44.1)	712 (49.3)	679 (48.6)	287 (47.0)	392 (49.8)
Multiple	58 (1.9)	34 (2.2)	24 (1.7)	20 (1.4)	8 (1.3)	12 (1.5)
White	75 (2.5)	38 (2.4)	37 (2.6)	29 (2.1)	17 (2.8)	12 (1.5)
Other[a]	22 (0.7)	14 (0.9)	8 (0.6)	11 (0.8)	7 (1.1)	4 (0.5)
Missing	954 (31.8)	514 (33.1)	440 (30.5)	427 (30.5)	180 (29.5)	247 (31.4)
Age at baseline, mean (SD), y	6.6 (1.2)	6.6 (1.3)	6.7 (1.2)	6.6 (1.2)	6.6 (1.2)	6.7 (1.2)
Untreated decay	874 (29.2)	482 (31.0)	392 (27.1)	413 (29.5)	193 (31.6)	220 (28.0)
Sealants at baseline	314 (10.5)	144 (9.3)	170 (11.8)	156 (11.2)	60 (9.8)	96 (12.2)
Decayed teeth, mean (SD)	0.7 (1.4)	0.7 (1.5)	0.6 (1.4)	0.7 (1.4)	0.7 (1.4)	0.7 (1.4)

[a] Other includes any other race not listed, including American Indian or Alaskan Native and Hawaiian or Pacific Islander.

The mean (SE) proportion of children with all caries remaining arrested was 0.56 (0.04) in the experimental group and 0.46 (0.04) in the control group, for a difference of −0.11 (95% CI, −0.22 to 0.01) (**Table 2**). The mean (SE) proportion of children without caries at baseline who remained caries free at follow-up was 0.81 (0.02) in the experimental group and 0.82 (0.02) in the control group, for a difference of 0.01 (95% CI, −0.04 to 0.06). Results from analyses using bootstrapped 95% CIs were not appreciably different for either caries arrest (difference between groups, −0.11; 95% CI, −0.27 to 0.002) or caries prevention (difference between groups, 0.01; 95% CI, −0.04 to 0.06). Experimental group rates were noninferior to those of the active control. Noninferiority for clinical outcomes is summarized in **Figure 2**.

With imputed data for children with caries arrest (n = 874), the estimated control proportion of caries arrest was 0.47, yielding a corresponding odds ratio (OR) noninferiority margin of approximately 0.6. Comparisons of the estimated treatment effect OR to 1/OR noninferiority margin indicates that the experimental treatment remained noninferior for caries arrest (OR, 1.49; 95% CI, 0.91-2.44) (**Table 3**). With imputed data for children with caries prevention (n = 2124), the estimated active control proportion of prevention was 0.81, for a corresponding OR noninferiority margin of 0.55. The estimated effect for prevention (OR, 0.93; 95% CI, 0.68-1.27) was similarly noninferior.

Figure 1. Study Flow Diagram

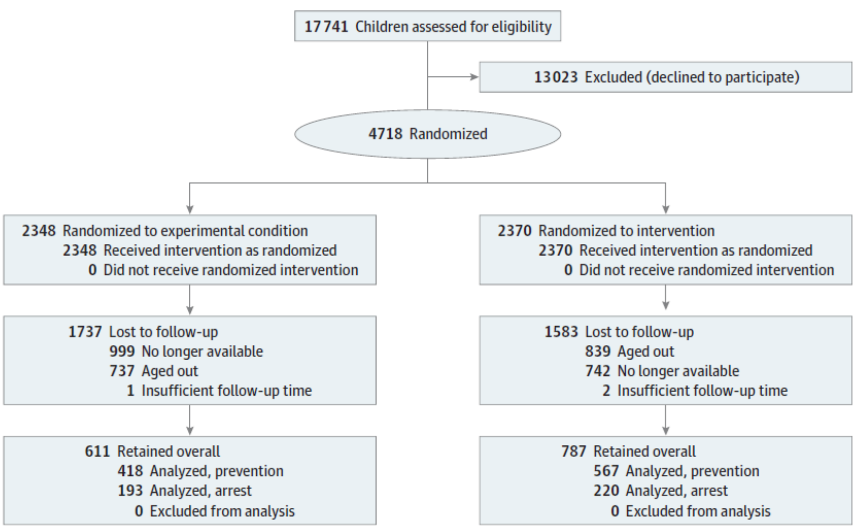
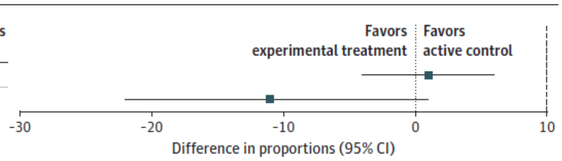


Table 2. Noninferiority Results for Caries Arrest and Prevention After 2 Years

	Experimental group			Control group			Difference			
Outcome	No. (mean)	SD	SE	No. (mean)	SD	SE	No. (mean)	SD	SE	95% CI
Caries arrest	193 (0.56)	0.50	0.04	220 (0.46)	0.50	0.04	413 (-0.11)	1.24	0.06	-0.22 to 0.01
Caries prevention	418 (0.81)	0.39	0.02	567 (0.82)	0.39	0.02	985 (0.01)	0.78	0.03	-0.04 to 0.06

Figure 2. Noninferiority Plot for Caries Arrest and Prevention at 2 Years

Outcome	Difference in proportions (95% CI)
Caries prevention	0.01 (-0.04 to 0.06)
Caries arrest	-0.11 (-0.22 to 0.01)



Whiskers indicate the 95% CI comparing the experimental group with the active control for caries arrest and prevention. The dashed line denotes the noninferiority limit. If the right-sided 95% CI does not exceed this threshold, then noninferiority is determined. This is equivalent to a 1-sided test.

Discussion

In this randomized clinical trial of SDF vs dental sealants, an experimental treatment of SDF and fluoride varnish was noninferior in the 2-year arrest and prevention of dental caries compared with a standard active comparator, a package of glass ionomer sealants and atraumatic restorations and fluoride varnish. The arrest rate for the experimental treatment was considerably higher than for the active control, and the upper bound for the arrest difference of 0.01 nearly demonstrated superiority.

Without proper and timely intervention, dental caries and other oral diseases can lead to severe systemic infections,[30] may negatively affect oral health-related quality of life,[31] and are associated with decreased student academic performance and school attendance.[32] To address the high rate of untreated caries in high-risk populations, the Centers for Disease Control and Prevention recommends school-based sealant programs, which have demonstrated clinical effectiveness and cost effectiveness.[33-35] Our results potentially support the use of SDF as an arresting and preventive agent for school-based oral health programs and complement previous findings from other studies of nonrestorative treatments in schools.[24]

Overall, we showed that SDF and sealants had an approximate 80% caries prevention rate and 50% caries arrest rate after 2 years. These findings are comparable to those from other more controlled clinical studies, which indicated no differences in the 6- and 12-month caries arrest rates comparing SDF vs atraumatic restorative treatment.[19] In addition, a prior review on the effect of SDF in preventing caries in primary dentition showed significant reductions in the development of new caries vs placebo after 24 months and was not more or less effective after 12 months compared with glass ionomer sealants.[15] Our randomized design and ethnically diverse student population supports the generalizability of results to urban primary schools.

Limitations

This study has some limitations. Our analysis classified each study participant as positive or negative for caries prevention or arrest and thus did not distinguish between single tooth failure and multiple tooth failures. This classification was done to ensure that the comparison for study outcomes was conservative, wherein any instance of failure at the tooth level would be considered failure at the individual level, regardless of how many failures were actually observed, and is in accordance with prior studies of school-based caries prevention.[24] Future analyses of CariedAway incorporating longer periods of follow-up will subsequently consider alternative definitions of failure, analyzing the rate of failure at both the tooth and surface levels. These analyses will also provide data on whether the severity of baseline decay is a moderator in the overall effectiveness of treatment.

The approximate 2-year gap between initial treatment and follow-up coincided with municipal policies stemming from COVID-19 infection rates in New York City, with baseline observations being conducted over a 6-month period from September 2019 to March 2020. On March 16, 2020, schools were closed citywide, and dental offices suspended care except for emergency procedures. Schools remained closed to all school-based health programs throughout the 2020-2021 academic year. The original study protocol stipulated that children would be followed up biannually, but the resulting gap in observation from baseline to first follow-up was 2 years. Although our analysis of primary outcomes for caries arrest and prevention at 2 years was not disrupted, the gap in observation meant that treated teeth could be exfoliated prior to follow-up and thus could not be included in analysis. In addition, only 47 of the originally proposed 60 schools were enrolled. This resulted in slight differences in total treatment group enrollment and baseline attributes; however, as the study

Table 3. Noninferiority Results for Caries Arrest and Prevention After 2 Years, Imputed

Outcome	No.	Odds ratio[a]	SE	*t* Value	*P* value	95% CI
Caries arrest	874	1.49	0.33	1.79	.10	0.91-2.44
Caries prevention	2124	0.93	0.14	−0.51	.62	0.68-1.27

[a] Odds ratio estimates compare experimental vs active control for each outcome.

analyzed caries arrest and prevention in isolation, these concerns are attenuated. Furthermore, preliminary power calculations for CariedAway estimated a necessary sample size of 396 that we artificially inflated by an a priori assumption of an intraclass correlation coefficient of 0.10, reflecting a moderate expectation of cluster correlation.[21] As we have shown, the actual degree of cluster correlation within schools is negligible. As a result, differences in the total study population should not have an appreciable effect on power.

Due to the continued effect of COVID-19, our follow-up rates among viable enrolled children was 46.6% (1398 of 2998). To partially address this limitation, we supplemented our original analysis with multiple imputation, and the results in the imputed sample were not different from those of the sample with completed follow-up observations. Despite this finding, our results should be interpreted with caution. Future longitudinal analysis of the CariedAway data will use all available observations of enrolled children to further expand on the presented analysis.

New York City dental offices were authorized to reopen in June 2020 after the adoption of interim infection control and prevention guidelines, specifically the reduction of aerosol-generating procedures. Due to these restrictions on preventive care, combined with the CariedAway population being specifically chosen because of their traditional lack of access to or use of routine dental care, it is unlikely that confounding dental treatments were received in the time between observations.[36] We further attempted to adjust for this in the analysis of caries arrest and prevention by considering both untreated decay and any new fillings that were not present at baseline, which would be indicative of new disease incidence prior to follow-up.

Conclusions

The benefits of the caries arrest and prevention methods tested in CariedAway offer opportunity for expanding access to critical oral health care worldwide. As school-based dental sealant programs are limited by burdening costs and lack of available, trained clinicians,[17] use of SDF may offer an attractive alternative approach to school-based caries prevention.

ARTICLE INFORMATION

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Data Sharing Statement: See Supplement 2.

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SUPPLEMENT 1.
Trial Protocol

SUPPLEMENT 2.
Data Sharing Statement

Additional Articles of Interest

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