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Practitioner's guide to fluoride

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Fluoride has been the cornerstone for dental caries prevention saving the United States an estimated $40 billion in oral health care delivery over the past 40 years [1]. Dental caries is a multi-factorial infection of the teeth characterized by demineralization of the dental hard tissues caused by repeated acid attacks with the potential for remineralization. Demineralization can progress, causing loss of tooth structure. Once cavitation occurs, there is no healing mechanism that can replace lost tooth structure [2,3].

Fluoride exerts its caries-protective properties in several ways. The primary anticaries effect is topical (posteruptive) [4,5]. Fluoride concentrated in plaque and saliva can inhibit the demineralization of enamel [6,7]. Fluoride taken up, along with calcium and phosphate by demineralized enamel (remineralization), forms an enamel crystalline structure that is more resistant to bacterial acid dissolution [6,8–12].

The systemic incorporation of fluoride into the developing enamel is thought to provide caries inhibition; however, evidence suggests that systemic fluoride (preeruptive) plays a more minor role in caries inhibition than previously thought [11]. The systemic ingestion of fluoride may also have a topical effect on enamel by passing through the digestive tract to the serum and then to the saliva [13].

Fluoride has been shown to inhibit the process by which cariogenic bacteria metabolize carbohydrates to produce acid and affect the bacterial

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production of adhesive polysaccharides [14]. The current view, however, is that fluoride's antibacterial effects occur at higher levels than those that prevail in the oral cavity [15].

Prescription fluorides

Dietary fluoride supplements

Fluoridated drinking water is the most effective and efficient strategy to reduce dental caries [16]. Supplements were designed to mimic the effects of fluoridated water. Since around 1950, fluoride supplements have been used in areas where there is little or no fluoride in the drinking water [17]. There is mixed opinion regarding the use of fluoride supplementation for caries prevention. Although there is evidence supporting the incorporation of fluoride into developing enamel [18–20], the systemic or preeruptive effect may play a modest role in caries prevention. Research suggests that fluoride's primary effect is topical or posteruptive [5].

Supplements can be as effective as fluoridated water in preventing caries [11,21,22]. There is concern, however, regarding the risk of enamel fluorosis. The prevalence of fluorosis has increased [23–25], and numerous studies have reported the association between supplementation and fluorosis [12,26–41]. Determination of the appropriate dosage schedule is based on the concentration of fluoride in the community drinking water and the age of the child. The current fluoride schedule has been jointly recommended by the American Dental Association (ADA), the American Academy of Pediatric Dentistry (AAPD), and the American Academy of Pediatrics (AAP) since 1994 [42–45] (Table 1). It is important to know the concentration of fluoride in the child's primary drinking water and from other sources (eg, day care, baby sitter, school, or bottled water) prior to supplementation. The fluoride concentration of community water can be determined by contacting the local water supplier or the local or state department of health. If the child's drinking water is from another source (eg, private well or bottled water), testing may be available through the local or state department of health, private laboratories, or dental schools. Fluoride acquisition indirectly by consuming foods and beverages processed in fluoridated areas is known as the "halo or diffusion" effect [46]. Practitioners should be aware

Table 1
Dietary fluoride supplementation schedule

Age	Less than 0.3 ppm F	0.3–0.6 ppm F	More than 0.6 ppm F
Birth–6 mos	0	0	0
6 mos–3 yrs	0.25 mg	0	0
3 yrs–6 yrs	0.50 mg	0.25 mg	0
6 yrs–up to at least 16 yrs	1.0 mg	0.50 mg	0

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that the distillation and reverse-osmosis home-water filtration systems may remove 90% or more of the fluoride; whereas, the less expensive carbon or charcoal filter systems remove little, if any, fluoride [47–49].

A dentist or physician must prescribe dietary fluoride supplements. Fluoride supplements are available in liquid, tablet, and lozenge form both with and without vitamins (Table 2). The fluoride-vitamin combination may improve parental compliance, thereby providing a greater benefit [50]. Fluoride tablets and lozenges should remain in contact with the teeth for as long as possible before swallowing (chew and swish or dissolve) to maximize both the topical and systemic effect. The primary teeth of children 1–6 years old would benefit from the posteruptive effect of fluoride, and the

Table 2
Common fluoride compounds

Compound		Fluoride content	pH
Supplements:			
0.275 mg NaF	Drops	0.125 mg F	Neutral
0.55 mg NaF	Drops, tablets, lozenges	0.25 mg F	Neutral
1.1 mg NaF	Drops, tablets, lozenges	0.5 mg F	Neutral
2.2 mg NaF	Tablets, lozenges	1.0 mg F	Neutral
Fluoride supplements may be combined with vitamins:			
0.022% APF	Rinse	200 ppm	Acid
Professionally applied:			
0.31% APF		3100 ppm	Acid
&	Sequential rinse	&	
0.1% SnF_2		1000 ppm	
2.0% NaF	Gel, foam	9040 ppm	Neutral
1.23% APF	Gel, foam	12,300 ppm	Acid
8.00% SnF_2	Rinse	19,400 ppm	Acid
0.4–2% NaF or APF	Prophy paste	4000–20,000 ppm	Neutral or acid
5.0% NaF	Varnish	22,600 ppm	Neutral
Self applied rinses:			
0.05% NaF	Daily	230 ppm	Neutral
0.1% SnF_2	Daily	240 ppm	Acid
0.2% NaF	Weekly (Rx)	905 ppm	Neutral
0.1% APF	Weekly (Rx)	1000 ppm	Acid
Self applied gels:			
0.4% SnF_2		970 ppm	Acid
1.1% NaF	(Rx)	5000 ppm	Neutral
1.1% APF	(Rx)	5000 ppm	Acid
Dentifrices:			
0.13–0.15%	NaF	1000–1500 ppm	Neutral
0.12–0.15%	Na_2FPO_3 (MFP)	1000–1500 ppm	Neutral

Supplements are intended for children <16 years old. Professional topical fluoride applications or prophylaxis use about 5 g or 5 mL of compound. Mouthrinsing uses about 5–10 mL of solution. Toothbrushing uses about 1 g of material per brushing. Fluoride contents are approximate values. This list is not intended to be comprehensive.

developing permanent teeth may derive some preeruptive benefit; however, fluoride supplements could also increase the risk for enamel fluorosis [51,52]. Fluoride supplements taken after the teeth erupt in children 6–16 years old reduce caries experience [53–55].

There is little support for prenatal fluoride supplementation because the use of fluoride supplements by pregnant women does not benefit their offspring [56], even though studies suggest fluoride can cross the placenta from mother to fetus [57,58].

Self-applied fluorides

Patients perceived to be at high risk for developing caries or who have experienced severe caries may receive additional topical fluoride. Risk factors may include orthodontic or prosthetic appliances, xerostomic patients (eg, head and neck radiation, medications, medical conditions such as Sjogren's syndrome), physically or mentally disabled patients unable to clean their teeth, poor diet, and hygiene. Fluoride mouthrinses and gels are concentrated fluoride preparations designed for home use.

Fluoride mouth rinses are designed for daily or weekly use in patients ≥ 6 years old. The age recommendation is due to an increased risk of ingestion and fluorosis. Fluoride rinses are available as stannous fluoride, acidulated phosphate fluoride, and sodium fluoride, which is the most common preparation. Several nonprescription or over-the-counter (OTC) preparations of 0.05% NaF are available for daily use. The 0.2% NaF preparation is a prescription mouthrinse intended for weekly use.

Studies from the 1970s and early 1980s indicated that fluoride mouthrinse reduced the caries experience among school children [59–66]. The National Preventive Dentistry Demonstration Program (NPDDP) compared the cost and effectiveness of combinations of caries-preventive procedures during 1976–1981 and documented only a limited reduction in dental caries attributed to fluoride mouthrinse, especially when children were also exposed to fluoridated water [67].

Fluoride gel is intended for daily use and is available as stannous fluoride and sodium fluoride (neutral and acidulated) preparations. Application is by custom tray or by brushing preferably at bedtime to allow prolonged exposure of fluoride to teeth. The research to support the efficacy of fluoride rinses and gels is promising but not definitive [68].

Restorative materials

Replacement of existing restorations accounts for almost 75% of all restorative procedures [69]. The reason most commonly cited for restoration replacement is secondary caries, which accounts for about 40% of such replacements [70]. In light of these observations and the known anti-caries activity of fluoride, fluoride has been incorporated into many restorative materials. The concept is for the fluoride-containing restorative material to release fluoride into the surrounding tooth, preventing demineralization [71] and enhancing remineralization of the enamel and dentin. Since the mid-1980s, a wide variety of fluoride-releasing dental restorative materials have been available to dentists and dental consumers [72]. The box below contains a list of several fluoride-containing materials. In vitro studies indicate that fluoride release from certain restorative materials can reduce the severity of recurrent caries [73–79]. Caries inhibition and remineralization potential have been shown in vitro by many fluoride-containing restorative materials when release levels have been equal to or exceeded 1 μg/mL [72]. All fluoride-containing materials release fluoride in an initial burst and then reduce exponentially to a much lower steady-state level of release [72]. Various types of aesthetic restorative dental materials showed a potential for fluoride recharge [80] after exposure to external sources of fluoride (ie, topical fluoride applications). The recharging effect of the restorative material is thought to occur when external fluoride is incorporated into the restorative material and then re-released.

Because of the small number of controlled clinical studies, it is difficult to say with certainty whether fluoride-releasing dental materials increase the remineralization of carious enamel and dentin, and whether these materials increase the resistance of enamel and dentin to caries [68]. Long-term, controlled clinical trials are needed to determine if fluoride incorporated into dental materials inhibits or reduces dental caries.

Professionally applied fluorides

For over 50 years, professionally applied topical fluorides have been used in dental offices. The premise for their efficacy was based primarily on the assumption that the fluoride would be incorporated into the crystalline

Fluoride containing dental materials

- Adhesives/bonding agents
- Bases and liners
- Bleaching/whitening materials (home and in-office products)
- Cavity varnishes
- Cements
  Temporary (ie, ZOE, ZnPO4)
  Permanent (ie, GI/hybrids, polycarboxylate, ZOE, ZnPO4)
- Compomers
- Composite resin materials
- Core build-up materials
- Sealants

structure of the enamel, and with the incorporation of the fluoride, the enamel would become more resistant to acid destruction [81]. Traditionally, the topical fluoride would be applied following the prophylaxis to ensure a cleaner surface for its uptake. Recent evidence has suggested, however, that high concentrations of fluoride are not incorporated into the crystalline structure of enamel [81]. Rather, fluoride combines with calcium from the enamel to form a salt that adheres to the enamel surface. When the pH in the mouth becomes acidic, fluoride is released [82]. Presently, a professional cleaning is unwarranted to prepare the teeth to receive fluoride.

Fluoride gels and foams

Professionally applied fluoride gels and foams deliver a high concentration of fluoride (9040–12,300 parts per million [ppm]) at a low frequency (annual or semiannual application). In early clinical studies, professionally applied topical fluoride gels had shown to reduce dental caries effectively [83]. Recently, the caries reduction has decreased to 26%, with its primary effect on permanent teeth of children living in nonfluoridated areas [62,84,85]. Additionally, the optimal interval between professionally applied fluorides has not been established through clinical trials. Studies regarding these topical fluorides in the prevention of dental caries have been mixed at best [86]. According to the latest evidence, semiannual frequency can be recommended for children who will benefit from the therapy [86].

Fluoride foams (1.23% APF and 2% NaF) were introduced to dental professionals in 1993. Several advantages exist for using the foam. They include:

(1) requiring a smaller quantity of fluoride to fill the tray
(2) decreased risk of fluoride ingestion
(3) less clogging of suction lines in the dental operatory [84].

Additionally, the foamy consistency may have a greater appeal for the pediatric population. The enamel uptake of the foam is similar to the gel preparation [87].

Whether to apply the topical fluoride for 4 minutes or 1 minute has not been proven in human clinical trials [67]. During the first minute of application is when the greatest percentage of fluoride uptake occurs [85]. Certainly, a 1-minute topical fluoride application would be desirous for the younger population, but the evidence has not been demonstrated to make this recommendation.

Fluoride prophylaxis pastes

Many prophylaxis pastes containing fluoride ranging from 4000–20,000 ppm are used professionally. None of these pastes has been recommended, however, by the Food and Drug Administration (FDA) or the ADA as caries preventive products. Except for several Scandinavian studies involving a professional prophylaxis with a fluoridated paste (2200 ppm) every 2–4 weeks, no data document efficacy from annual or semiannual use of the pastes [88–90]. Even though chronic fluoride ingestion rarely occurs, the wide range of fluoride content in these products is without any basis [91]. Manufacturers of these types of fluoride products should be required to justify their recommendations.

Fluoride varnishes

Fluoride varnishes were developed as alternative topical products to the conventional fluoride gels and foams. They first appeared in Europe in 1964 as a 2.26% fluoride product and have had wide acceptance in Europe and Canada to prevent dental caries [92]. For almost 30 years in Europe, fluoride varnishes have been the modality of choice for professionally applied topical fluorides [93]. The premise for their effectiveness is the adherence of a high concentration of fluoride onto the enamel for up to 24 hours. Fluoride is deposited as calcium fluoride, and its ions are slowly released into the oral cavity. Advantages of the varnishes include an acceptable taste, rapid setting time, ease of application, and use of smaller amounts of fluoride when compared with professionally applied topical gels and foams [94].

Two types of varnishes, sodium fluoride or a difluorosilane, are available in the United States today. Their approval from the FDA is for use as a cavity varnish or as a dentinal hypersensitivity agent [95]. Because caries prevention is considered to be a drug claim, manufacturers of fluoride varnishes would need to submit evidence from clinical trials to receive FDA approval as anticaries agents [96]. In the United States the therapeutic use of fluoride varnishes for caries prevention is referred to as "off-label" because the product is being used for purposes other than originally approved [97]. This does not imply that professionally applied fluoride varnishes for caries prevention are illegal or unethical practices. Studies by Weinstein et al and Domoto et al have demonstrated promising caries prevention results [98,99]. In Washington and North Carolina, treatment with fluoride varnishes is a Medicaid-covered service [100]. In the near future, fluoride varnishes should become a vital part of the caries prevention plan.

Fluoride varnishes are applied onto the fissures, proximal surfaces of primary molars, and sometimes incisors with a small disposal brush and a saliva ejector. The frequency of application is based on the patient's caries risk assessment. The most frequently prescribed regimen is a semiannual application [101]. In order for fluoride varnishes to be effective, reapplication is required. Professional prophylaxis of the teeth is not essential prior to varnish application, even though most manufacturers recommend one. This ease of application makes it quite attractive for use with precooperative pediatric dental patients. The teeth should be dried with compressed air or with cotton gauze. Then, the varnish is applied and sets on contact with oral fluids.

Fluoride varnishes are another modality to deliver and retain fluoride onto the enamel surface of teeth. Varnishes may provide an alternative for caries control in patients with special needs, those receiving head and neck radiation, those undergoing orthodontic treatment, and those on chronic oral medications [100]. As more clinical trials are completed in the United States, fluoride varnishes should become an important component of caries prevention.

OTC fluorides

Fluoride has been incorporated into OTC, commercial dentifrices for over 40 years and accounts for approximately 98% of all dentifrices sold in the United States [102]. The use of OTC fluoride dentifrices along with community water fluoridation correlates with a significant decline in caries prevalence and extent among children and young adults [103–106]. Children in the United States have experienced a 36% decline in mean decayed, missing, and filled surfaces (DMFS) between 1980 and 1986 [107]. This reduction in caries is largely attributed to declines in smooth surface caries when compared with occlusal surfaces [108]. Individuals at greatest risk for caries include those without access to an optimally fluoridated water supply and those of lower socioeconomic status [109]. As a public health measure, fluoride in community water supplies and fluoride dentifrices have been repeatedly demonstrated as the most cost-effective measures for preventing dental caries [110].

Effectiveness of OTC preparations compared with placebos has demonstrated the effectiveness of fluoride dentifrices in caries reduction. In a review of published 2–3 year clinical studies comparing placebo and 0.243% sodium fluoride (NaF) dentifrices, Biesbrock found a mean dental caries reduction of 32% [111]. Fluoride dentifrices in the United States usually contain sodium fluoride (NaF) or sodium monofluorophosphate (MFP). In their review of studies comparing NaF and MFP formulations, Stookey et al concluded that NaF was significantly more effective than MFP in preventing caries by 5–10% in trials of 2–3 years duration [110]. Finally, a significant dose response of decreasing incident caries with increasing fluoride concentrations in dentifrices has been found for both NaF [111,112] and MFP [113,114]. A twofold or more concentration of currently marketed fluorides were compared in these trials, and the reduction of incident caries was in the range of 12–20% over the 3 years of the study, with a significant reduction in occlusal caries [103,111,113,114].

High fluoride products may be beneficial to individuals at high risk for caries, including those living in nonfluoridated areas. High fluoride dentifrices are counter-indicated, however, for use in the general population where fluoridated drinking water is available and among young children, where the risk of dental fluorosis may be high. In a review of fluoride dentifrice use in early childhood with subsequent development of dental fluorosis, summarized results of these studies conducted since the 1990s have identified an association between dental fluorosis and the use of fluoride dentifrice [115]. Findings from studies of lower-dose fluoride dentifrices' anticaries activity also were reviewed by these researchers. They concluded that there are important gaps in the knowledge about the effectiveness of lower-concentration fluoride dentifrices and their use.

Daily use of OTC fluoride mouthrinses used in conjunction with fluoride dentifrices has demonstrated additional benefit in caries reduction [116,117]. Currently, 0.05% NaF rinses are available and have shown a 65% reduction in caries when used twice daily [116] and appear particularly efficacious in root caries reduction [117]. Caries incidence is reduced generally by about 10–20% when rinses are utilized in unsupervised oral hygiene as an adjunct to fluoride dentifrices [117].

Ideally, loosely bound fluoride reservoirs that can maintain the concentration of fluoride in the oral cavity following product use would have a significant impact on caries inhibition [118–120]. Currently, controlled-release fluoride rinses and dentifrices are being evaluated for their effectiveness for sustained bioavailability in salivary fluoride to improve the de- and remineralization processes. Current findings indicate that a lower-concentrated fluoride dentifrice with controlled release of fluoride that can be incorporated into dental plaque when acidified to a critical pH may be appropriate for caries prevention [119]. This dentifrice could be developed in the near future as an effective OTC product [119].

Toxicity

Fluoride's caries preventive effects are well known; however, the potential toxic effects of fluoride must be considered. The optimal daily fluoride intake is considered to be 0.05–0.07 mg F/kg of body weight [46]. Ingestion of large amounts of fluoride may cause acute toxic reactions involving the gastrointestinal, neurological, cardiovascular, and blood chemistry systems and ultimately death [121–123]. Toxic reactions may occur with ingestion of about 5–8 mg F/kg [124,125]. A certainly lethal dose is considered to be 32–64 mg F/kg [124].

Dental fluorosis occurs as a result of excessive ingestion of fluoride during tooth development [126]. The severity of the fluorosis depends on the dose, duration, and timing of the fluoride ingestion [127]. Because enamel is not susceptible to fluorosis once its pre-eruptive maturation is complete, the risk of fluorosis is limited to children $\leq$8 years old [128]. Regardless of the severity, enamel fluorosis is considered a cosmetic rather than a functional effect [24,128–130].

Skeletal fluorosis, a crippling bone disease, has been associated with high levels of fluoride. Bone health, according to accepted scientific knowledge, is not adversely affected by ingestion of optimally fluoridated water [131–135]. Ingestion of fluoride has also been suggested to cause cancer; however, the American Cancer Society has stated "Scientific studies show no connection between cancer rate in humans and adding fluoride to drinking water" [136]. Several reviews have also concluded that there is no relationship between fluoridation and cancer [137–140].

Caution must be exercised with all fluoride-containing products, especially professionally applied fluoride treatments that may pose the greatest risk of acute toxicity. Practitioners prescribing or administering fluoride need to be aware of the potential acute and chronic toxic reactions associated with the various treatment modalities.

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