

Association Between Self-Reported Dental Hygiene Practices and Dental Procedure-Related Recurrent Angioedema Attacks in HAE Subjects: A Multicenter Survey



Umesh Singh, MD, PhD, MPH^a, William R. Lumry, MD^b, Paula Busse, MD^c, H. James Wedner, MD^d, Aleena Banerji, MD^e, Timothy J. Craig, MD^f, H. Henry Li, MD^g, Raffi Tachdjian, MD^h, Joshua S. Jacobs, MDⁱ, Marc A. Riedl, MD^j, Mark Davis-Lorton, MD^k, Sandra C. Christiansen, MD^j, Bruce L. Zuraw, MD^j, and Jonathan A. Bernstein, MD^a *Cincinnati, Ohio; Dallas, Texas; New York and Mineola, NY; St. Louis, Mo; Boston, Mass; Hershey, Pa; Chevy Chase, Md; and Los Angeles, Walnut Creek, and La Jolla, Calif*

What is already known about this topic? Dental procedures may trigger an angioedema attack in hereditary angioedema (HAE) patients with moderate-to-severe disease.

What does this article add to our knowledge? One of the most significant covariates that are significantly associated with recurrent angioedema attacks in patients with HAE is the frequency of routine preventive dental visits among these patients.

How does this study impact current management guidelines? For patients with HAE, routine preventive dental visits every 6 months may be preferable. However, to make this a recommendation for routine clinical practice, randomized controlled trials or self-controlled pre- and postintervention assessments combined with assessment of their dental providers investigating the association between the frequency of dental visits and severity of periodontal/gingival disease with recurrent angioedema attacks should be conducted.

^aDivision of Immunology/Allergy, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio

^bAllergy and Asthma Research Associates Research Center, Dallas, Texas

^cDivision of Clinical Immunology, Mount Sinai, New York, NY

^dAllergy and Immunology, Washington University School of Medicine, St. Louis, Mo

^eDivision of Rheumatology, Department of Allergy & Immunology, Massachusetts General Hospital, Boston, Mass

^fDepartment of Medicine and Pediatrics, Penn State University, Hershey, Pa

^gInstitute for Asthma and Allergy, PC, Chevy Chase, Md

^hDivision of Allergy and Immunology, UCLA School of Medicine, Los Angeles, Calif

ⁱAllergy and Asthma Clinical Research, Inc., Walnut Creek, Calif

^jDivision of Rheumatology, Allergy & Immunology, University of California, San Diego, La Jolla, Calif

^kDepartment of Medicine, Winthrop University Hospital, Mineola, NY

This study was supported by Shire/Takeda for an investigator-initiated study (J.A.B.).

Conflicts of interest: W. R. Lumry is on the Medical Advisory Board for US Hereditary Angioedema Association. P. Busse reports grants and personal fees from CSL Behring, Shire/Takeda, Pharming, BioCryst, Novartis, and ResTORbio; personal fees from Pearl Therapeutics, CVS Health, Law offices of Levin, Riback, Adelman, and Flangel, Astra Zeneca, GSK, Vedder Price, and Fresenius; and nonfinancial support from Hereditary Angioedema Association and American Academy of Allergy, Asthma, and Immunology, outside the submitted work. H. James Wedner reports grants and personal fees from BioCryst and CSL; and grants from Takeda, outside the submitted work. A. Banerji reports grants from Takeda and BioCryst; and personal fees from Takeda, BioCryst, CSL, Pharming, Kalvista, and Pharvaris, outside the submitted work. T. J. Craig reports grants, personal fees, and other from CSL Behring and Takeda; grants and personal fees from Dyax, BioCryst, and Pharming; personal fees from Grifols; and grants and nonfinancial support from GSK, Regeneron,

and Novartis/Genentech, outside the submitted work; and is on the Medical Advisory Board for HAE-A of America, AAAAI Board, and ALA Mid Atlantic Board. H. Henry Li reports grants, personal fees, and nonfinancial support from BioCryst, CSL Behring, Pharming, and Shire/Takeda, outside the submitted work. M. A. Riedl reports grants and personal fees from CSL Behring, Pharming, Takeda/Shire, and BioCryst; grants from Ionis; and personal fees from Adverum, Attune, Kalvista, and Pharvaris, outside the submitted work; and is on the US Hereditary Angioedema Association Medical Advisory Board (uncompensated). S. C. Christiansen reports grants from U. Cincinnati, during the conduct of the study; and personal fees from CSL Behring, Takeda, Pharming, and BioCryst, outside the submitted work. B. L. Zuraw reports grants from U. Cincinnati, during the conduct of the study; personal fees from CSL Behring, Takeda, Adverum, Pharming, BioCryst, and Attune; and other from Ionis, outside the submitted work. J. A. Bernstein reports personal fees for consulting, speaking, and serving as a principal investigator for Shire/Takeda, CSL Behring, and Pharming; reports consulting and speaker fees from Optinose; reports personal fees for speaking and serving as a sub-investigator for ALK and GlaxoSmithKline; reports personal fees outside the submitted work for consulting, speaking, and serving as a principal investigator for Astra Zeneca, Sanofi-Regeneron, and Novartis/Genentech; and is a consultant and principal investigator for Merck, Biocyst, Kalvista, and Ionis. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication October 3, 2019; revised May 1, 2020; accepted for publication May 20, 2020.

Available online June 10, 2020.

Corresponding author: Jonathan A. Bernstein, MD, Allergy Section, Division of Immunology, Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH. E-mail: bernstja@ucmail.uc.edu.

2213-2198

© 2020 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2020.05.041>

Abbreviations used

ADA- American Dental Association

AE- Angioedema

AIC- Akaike information criteria

C1-Inh- C1-esterase inhibitor

HAE- Hereditary angioedema

LTP- Long-term prophylaxis

STP- Short-term prophylaxis

BACKGROUND: Hereditary angioedema (HAE) symptoms may be triggered by dental procedures, thereby complicating dental care in individuals affected by the condition.

OBJECTIVE: This study investigated the self-perceived dental care needs, perceived susceptibility to acute angioedema (AE) attacks after dental procedures, and dental care behavior of patients with HAE.

METHODS: A self-administered semistructured web-based questionnaire was distributed to 250 adult patients with HAE (type 1 or 2; 88% type 1) and 256 matched non-HAE controls. Data were analyzed using stratified χ^2 tests, logistic regression, and classification trees.

RESULTS: A total of 46.4% of HAE versus 55.5% of control patients had dental visits within 6 months ($P = .04$). Dental insurance was a barrier to seeking routine dental visits among both groups. However, significantly fewer patients with HAE had routine dental visits within 6 months despite having dental insurance compared with control patients (48% vs 60%, $P = .01$). Within the HAE group, a significantly greater number of patients with dental visits at intervals greater than 6 months had a history of recurrent postprocedural AE attacks (odds ratio [OR]: 3.9 [1.7, 8.8], $P = .0005$) and used antibacterial toothpaste more frequently than those without recurrent AE attacks (OR: 4.7 [1.5, 15.4], $P = .005$).

CONCLUSIONS: These data support the hypothesis that patients with HAE who are predisposed to having AE episodes in response to medical or physical trauma visit the dentist less and engage in specific oral hygiene practices more frequently than matched control patients and patients with HAE who reported that they were less likely to swell after a dental procedure. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:3162-9)

Key words: Hereditary angioedema; Dental hygiene; Postdental procedure angioedema attacks; Health belief model; Teeth brushing frequency; Routine dental visit; Questionnaire survey

Hereditary angioedema (HAE) is an autosomal dominant disorder commonly caused by C1-esterase inhibitor (C1-Inh) deficiency, leading to bradykinin-mediated increased vascular permeability. It is manifested clinically as nonpruritic, nonpitting swelling of the submucosal tissues of the peripheral skin, face, gastrointestinal tract, and upper airways. Attacks involving the upper airways are life threatening and may be fatal.¹ Triggers of angioedema (AE) attacks are uncertain but include stress, infection, specific medications, and trauma. Nearly 54% of attacks have been reported to be related to trauma including dental, surgical, or medical procedures that can be exacerbated by anxiety about the possibility of swelling.^{2,3} Of note, severe

upper airway swelling attacks have been reported to be triggered by minor trauma or pressure during routine dental care procedures.⁴

The epidemiology of periodontal diseases in HAE subjects has not been reported previously. Furthermore, it has not been possible to determine the true causality or association between periodontal disease and postprocedural AE attacks during or immediately after dental procedures. However, HAE is believed to have a major impact on dental hygiene due to patient concerns about increased risk of swelling episodes. It has been hypothesized that HAE subjects with infrequent patterns of dental care are prone to having poorer oral health that can predispose them to gingivitis or periodontitis that further increases their susceptibility to dental procedure-related HAE attacks.⁵⁻⁷

Because of this possible association between periodontal disease and postprocedural AE attacks, many subjects with HAE may avoid routine dental care. With the advent of novel on-demand or preprocedural prophylactic therapies that can be used as short-term prophylaxis (STP) 1 to 2 hours before a dental procedure to mitigate or prevent upper airway swelling episodes, dental management and treatment of patients with HAE can be provided safely in an outpatient setting by dentists in conjunction with an HAE specialist.⁸⁻¹⁰

Despite dissemination of guideline recommendations for the management of HAE using STP before invasive medical and/or dental procedures, there is still a need to create awareness among patients with HAE and providers about the importance of routine dental care to maintain good oral hygiene and prevent related comorbidities that could seriously impact their overall health and disease activity. Ongoing concerns by patients with HAE about poor access to primary dental care because many dental professionals do not feel comfortable treating them and apprehension about triggering a swelling event are 2 possible reasons that could impact their dental care. Furthermore, although the American Dental Association (ADA) recommends that dental visit frequencies be tailored to the needs of specific individuals, there are still no specific recommendations regarding optimal dental visit frequency for patients with HAE.¹¹

Given these gaps in knowledge regarding dental hygiene that includes dental visit frequency and HAE, we used a web-based questionnaire to analyze perceptions by patients with HAE about personal dental care practices compared with a non-HAE matched case control cohort. Specifically, we investigated (1) the frequency and/or severity of procedure-related AE attacks; (2) the frequency of dental visits among HAE subjects compared with matched control subjects; (3) whether having HAE influences behavior for seeking dental health care; and (4) differences in oral hygiene practices among patients with HAE attributable to their concerns for postprocedural AE attacks compared with matched controls.

METHODS

The rationale for this study was based on the health belief model for oral health behaviors¹² applied specifically to HAE subjects who experience frequent AE attacks during or immediately after dental procedures^{13,14} (Figure 1). It was assumed that the dental hygiene practices adopted by HAE subjects are closely associated with the constructs of the health belief model such as perceived severity, self-efficacy, cues to action, perceived benefits, and perceived barriers of routine (preventive) dentist visits. Furthermore, it was assumed that

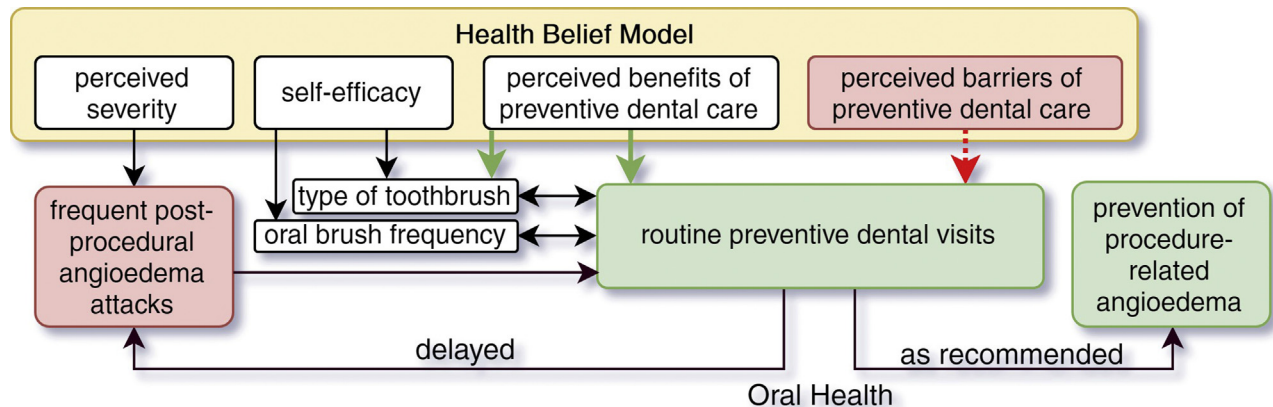


FIGURE 1. Rationale of this study was based on the Health Belief Model of health-related behaviors^{13,14} as applied to hereditary angioedema subjects for prevention of postprocedural angioedema attacks during or immediately after routine dental procedures.

the HAE subjects are aware of their susceptibility to AE attacks after procedure. Accordingly, oral care practices such as the frequency of oral brushing and the utilization of preventive care, such as frequency of routine dental visits contingent on access or affordability of dental care, may be closely associated. Less frequent dental visits by patients with HAE may affect their oral health and thus increase the frequency and/or severity of postprocedural AE attacks during or immediately after dental procedures.

Questionnaire development

A semistructured self-administered web-based questionnaire survey was designed on REDCap to elicit information on the dental hygiene practices and the incidence of dental procedure–related AE attacks from a sample of patients with HAE aged ≥ 18 , and from an age, gender, and ethnicity matched non-HAE control group within the United States. The intended clinical application of the survey questionnaire was very similar to in-person interviews or paper-based methods used in clinical research. Such web-based methods maintain data or information equivalence and avoid bias resulting from sociocultural differences among survey participants.¹⁵

The 92-item questionnaire designed for HAE subjects, and a 35-item questionnaire (ie, a subset of the 92-item questionnaire) for the matched control subjects, obtained cross-sectional information on the following parameters: the frequency of STP and long-term prophylaxis (LTP) among HAE subjects; between-group differences in the frequency of routine dental visits and dental care perceptions and practices, including their preferences on the use of specific dental hygiene products (such as fluoride or antibacterial toothpaste and motorized or manual toothbrush); reasons for deferral or avoidance of routine dental care; frequency, severity (subjective assessment), and anatomical sites of postprocedural AE attacks despite STP (ie, breakthrough attacks); frequency of HAE prodromes preceding postprocedural attacks; and differences in the prevalence of chronic comorbid conditions among the patients with HAE compared with the non-HAE patients. The questionnaire excluded sensitive personal information and was exempted from continuing oversight by the institutional review board at each participating site. The questionnaire survey was distributed by 14 HAE specialists (from 12 sites), all allergists, to previously diagnosed patients with HAE ($n = 250$) and matched non-HAE controls

($n = 256$) from their practice. An individual matching strategy was used for matching non-HAE controls with patients with HAE; controls were selected from the same general practice with the nearest date of birth, same gender, race, ethnicity compared with patients with HAE. These controls were being treated at those practices for clinical conditions other than AE or urticaria. Thus, potential sources of bias, such as age and race/ethnicity on the outcomes measure (ie, the frequency of dentist visits or health beliefs), were minimized or eliminated by individual matching.

Statistical analysis

Categorical and ordinal responses from HAE and control groups were analyzed using the χ^2 test. Logistic regression and classification tree analysis were used to determine significant differences in the routine dental care practices and dental visits between these groups. Cochran-Mantel-Haenszel statistics were used in multiway analysis stratified by frequency of brushing teeth and dental visit frequency to estimate the common odds ratios. Within-group analyses for patients with HAE were performed using these same methods; in addition, multivariable logistic regression analyses, with stepwise variable selection, for this group were conducted to determine the most significant determinants of recurrent postprocedure AE attacks. The best k-predictor regression model as per the least Akaike information criterion (AIC) value was determined. Analysis was adjusted for significant additional covariates such as severity of disease (as determined by history of being on LTP and severity of previous procedure-related AE attacks), having dentures, age, gender, race, frequency of teeth brushing, and dental insurance coverage. All statistical analyses were performed using SAS 9.4 (Cary, NC) and R (R Core Team, Vienna, Austria).

RESULTS

Between-group analyses

Demographics. The median age (quartiles) of patients with HAE ($n = 250$) was 41 (29, 53), and the median age (quartiles) of control patients ($n = 256$) was 43 (33, 56), $P = .13$. Most respondents with HAE reported their attacks beginning in their adolescence. Females comprised 66% of HAE and 72% of

TABLE I. Between-HAE and control group stratified analysis: cross-tabulation of dental visit frequency between groups stratified by dental insurance coverage and frequency of brushing teeth. Missing values for frequency of brushing teeth: Controls = 18, HAE = 31.

Stratification variable	Comparison group	Dental visit frequency		Row total	χ^2 test <i>P</i> value	McNemar's test <i>P</i> value	Common OR (control vs HAE)	Overall kappa coefficient (control vs HAE)
Dental insurance coverage		<6 mo	>6 mo					
Yes	Control	124 (60.5%)	81 (39.5%)	205	.01	.40	1.4 (1.0, 2.0)	0.08 (0.0, 0.2)
	HAE	92 (48.2%)	99 (51.8%)	191				
No	Control	18 (35.3%)	33 (64.7%)	51	.56	.23		
	HAE	24 (40.7%)	35 (59.3%)	59				
Frequency of brushing teeth								
≥2/d	Control	107 (60.5%)	70 (39.6%)	177	.11	.26	1.5 (1.0, 2.1)	0.1 (0.0, 0.2)
	HAE	84 (51.9%)	78 (48.2%)	162				
1/d	Control	25 (41%)	36 (59%)	61	.21	.001		
	HAE	17 (29.8%)	40 (70.2%)	57				

HAE, Hereditary angioedema; OR, odds ratio.

control group. Among patients with HAE, 88% were previously diagnosed as HAE type 1 and 12% as HAE type 2.

Routine dental visit frequency. The durations between dental visits were pooled into 2 categories, that is, “<6 months” and “>6 months” based on a heuristic approach using recursive partitioning (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org); more specific intervals were not attempted to maintain reasonable sample size between categories during statistical analysis. Based on this classification, the frequency of such visits between HAE and non-HAE (control) groups differed significantly ($P = .04$) with a greater percentage of control subjects (vs HAE group) having more frequent dental visits <6 months (55% vs 45%) and greater percentage of patients with HAE (vs controls) deferring such visits >6 months (54% vs 46%), $P = .04$.

Dental insurance coverage. A total of 76% of HAE and 80% of control patients had dental insurance coverage. Lack of dental insurance was a major barrier for both groups in seeking routine dental visits; 56.8% of patients with HAE and 59.4% of controls responded that dental insurance coverage influences their routine dental visits.

Dental hygiene habits. Patients with HAE used antibacterial toothpaste more frequently than matched controls (9.6% vs 4.3%; $P = .02$). There was no difference between the HAE and control groups with respect to wearing dentures. Among the HAE subjects ($n = 247$, missing data = 3), 66.4% (164 of 247) and 32.4% (80 of 247) reported using a manual and motorized toothbrush, respectively. Among controls ($n = 254$, n -missing = 2), 61.0% (155 of 254) and 38.2% (97 of 254) reported using a manual and motorized toothbrush, respectively. These differences were statistically not significant ($P = .37$). The difference between groups regarding the frequency of dental flossing/day was also not significant ($P = .7$).

Comorbidities. Comorbid health conditions such as hypertension, diabetes, hypercholesterolemia, chronic rhinitis, asthma, and non-HAE medications did not differ significantly between groups.

Tests of association between groups. A decision tree analysis determining factors significantly associated with the frequency of dental visits is illustrated in Figure E2 (available in this article's Online Repository at www.jaci-inpractice.org). Associations between constructs of the health belief model (ie, perceived benefits and self-efficacy, regarding oral health) were determined as follows.

Dental visit frequency between groups stratified by dental insurance coverage. Table I summarizes the results of the differences in dental visit frequency between HAE and control groups stratified by dental insurance coverage showing an overall significant difference in the frequency of dental visits between groups (common odds ratio = 1.4 [1.0, 2.0]) in the subgroups of HAE and control patients with dental insurance coverage ($n = 396$) but not in the subgroup without dental insurance ($n = 110$; 51 control, 59 HAE). Dental visits <6 months were reported by 48.2% of HAE versus 60.5% of controls ($P = .014$) in the subgroup with dental insurance, and by 40.7% of HAE versus 35.3% of controls ($P = .56$) in the subgroup without dental insurance. Thus, whereas HAE patients with dental insurance compared with control patients with dental insurance were less likely as a group to have more frequent dental visits, there was no difference between HAE and control patients without dental insurance regarding dental visit frequency, suggesting that routine preventive dental care was influenced more by poor access to this health care resource than HAE status. However, within the HAE group, concerns about swelling attacks and cost/insurance were both major reasons for delaying a dental visit.

Dental visit frequency between groups stratified by teeth brushing frequency

Approximately 65% of HAE and 69% of control patients brushed their teeth at least twice daily. However, a greater percentage of controls versus HAE subjects had dental visits <6 months even when stratified by teeth brushing frequency (Table I). The common odds ratio of 1.5 indicates that the probability of regular dental visits (ie, <6 months) for all patients with teeth brushing frequency ≥2/day is 1.5 times that probability for patients who brush teeth once daily. These results indicate that the constructs of the health belief model applied to

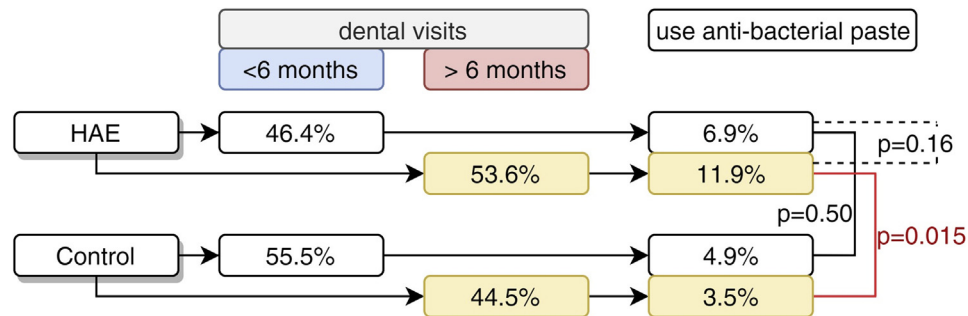


FIGURE 2. Relative percentages of HAE vs non-HAE control groups by frequency of routine dental visits and use of oral care product with antibacterial ingredients. A relatively greater percentage of HAE vs control patients had less frequent routine dental visits (46.4% vs 55.5%). The usage of toothpaste with antibacterial ingredients was greater among the subgroups of HAE (11.9%) vs control patients (3.5%) ($P = .015$) with less frequent dental visits (ie, >6-month intervals). HAE, Hereditary angioedema.

oral health behaviors, specifically pertaining to teeth brushing frequency and dental visits, are closely related. Those patients who have self-efficacy (ie, capable of completing the task of teeth brushing as recommended) and perceive the benefits of recommended dental care are more likely to have better utilization of routine preventive dental visits compared with those without these inherent traits.

Preference for antibacterial toothpaste and its association with dental visit frequency. To investigate further the increased use of antibacterial toothpaste among patients with HAE versus controls (9.6% vs 4.3%, $P = .02$) and dental visit frequency, a multiway analysis of the usage of antibacterial toothpaste between groups controlling for dental visit frequency (ie, <6 months vs >6 months) was performed (Figure 2). The results of this analysis demonstrated that there was a significantly higher usage of antibacterial toothpaste by patients with HAE compared with control patients (11.9% vs 3.5%, $P = .015$), which was only observed between the HAE and control subgroups with dental visits >6 months.

Within-HAE group analyses

Analyses of attack location, the presence or absence of a prodrome, and specific dental procedures associated with AE attacks are summarized in the text available in this article's Online Repository at www.jaci-inpractice.org and Tables E1-E3 (available in this article's Online Repository at www.jaci-inpractice.org).

Short- and long-term prophylaxis. A total of 48% (120 of 250) of the HAE subjects reported receiving STP before dental procedures, and among these patients, 47.5% (57 of 120) endorsed a history of AE attacks during/after a dental procedure. A C1-inhibitor product was used most frequently (80.8%) as the STP agent and was administered mostly before a cavity filling (72%) and root canal treatment (59%) (data not included).

A total of 157 HAE subjects were on LTP, of whom 59% (93 of 157) were using a C1-inhibitor replacement therapy. Between 50% and 69% of HAE subjects on LTP received STP before dental procedures. The rates of AE attacks (unadjusted for the severity of disease) despite being on LTP and being administered STP ranged between 19% for those on either C1-Inhibitors or danazol as LTP and 50% for those on tranexamic acid as LTP.

Association between recurrent AE attack and dental visit frequency: unadjusted analysis.

Individual risk factors that determine the frequency of dental visits may be a comorbid condition for recurrent postprocedural AE attacks. Therefore, associations between delayed preventive dental visits that may predispose to increases in periodontal disease and the history of recurrent postprocedural AE attacks in patients with HAE were investigated. Approximately 45% (112 of 250) of patients with HAE had routine dental visits >6 months, as shown by row totals (72 + 40 = 112) in Table II. Recurrent postprocedural AE attacks were reported by 21% (ie, 24 of 112) of these subjects, but only by 7% (ie, 9 of 138) of HAE subjects who had routine dental visits <6 months ($P = .0005$) (Table II). The unadjusted odds ratio for the association of a recurrent postprocedural AE attack and delayed dental visit was 3.9 (1.7, 8.8). Based on this analysis, it appears that patients with HAE with recurrent postprocedural AE attacks are delaying preventive dental care visits due to concerns of experiencing an AE attack.

Association of recurrent postprocedural AE attacks and dental visits stratified by dental insurance coverage.

Not having dental insurance was a distinct barrier to regular dental visits <6 months. Only 32% (19 of 59) of those without dental insurance versus 62% (119 of 191) of those with dental insurance had dental visits <6 months ($P < .0001$). Therefore, the association between recurrent AE attacks and frequency of dental visits was stratified on dental insurance coverage. Table II shows that the common odds ratio for recurrent AE attacks in patients with dental visits >6 months versus <6 months is 5.0 (confidence interval: 2.1, 11.8).

Associations of recurrent postprocedural AE attacks and dental visits stratified by teeth brushing frequency.

The frequency of dental visits was significantly associated with teeth brushing frequencies; 64.7% (119 of 184) of patients with HAE reporting at least twice daily teeth brushing versus 31.6% (18 of 57) reporting once daily teeth brushing had dental visits <6 months ($P < .0001$) (Table II). The common odds ratio of recurrent AE attacks adjusted for the frequency of teeth brushing was 3.6 (1.5, 8.6) for patients with HAE with dental visits >6 months (vs patients with HAE with dental visits <6 months), suggesting that the frequency of dental visits is an

TABLE II. Within-HAE group stratified analysis: cross-tabulations showing associations of the frequency of recurrent acute angioedema attacks with dental visit frequency stratified by dental insurance coverage and frequency of brushing teeth

Attacks with dental visit frequency stratified by dental insurance coverage and frequency of brushing teeth								
Stratification variable	Determinant	Outcome variable		Row total	McNemar's test <i>P</i> value	χ^2 test <i>P</i> value	Common odds ratio*	Overall kappa coefficient
	Dental visit frequency (mo)	Recurrent attacks						
		Yes	No					
Dental insurance coverage								
Yes	>6	19 (26.4%)	53 (73.6%)	72	<.0001	.0004	5.0 (2.1, 11.8)	0.12 (0.05, 0.19)
	<6	9 (7.6%)	110 (92.4%)	119				
No	>6	5 (12.5%)	35 (87.5%)	40	<.0001	.1	<i>P</i> < .0001	
	<6	0 (0%)	19 (100%)	19				
Teeth brushing frequency [†]								
2/d	>6	12 (18.5%)	53 (81.5%)	65	<.0001	.02	3.6 (1.5, 8.6)	0.12 (0.04, 0.20)
	<6	8 (6.7%)	111 (93.3%)	119				
1/d	>6	10 (25.6%)	29 (74.4%)	39	<.0001	.07	<i>P</i> < .003	
	<6	1 (5.6%)	17 (94.4%)	18				

HAE, Hereditary angioedema.

*Odds of recurrent acute attack among subjects with dental visit frequency >6 months.

†Number of missing values for teeth brushing frequency >6 months = 8 and for <6 months = 1.

Stratification by Long-Term Prophylaxis (LTP) and History of Post-Procedural Angioedema Attack

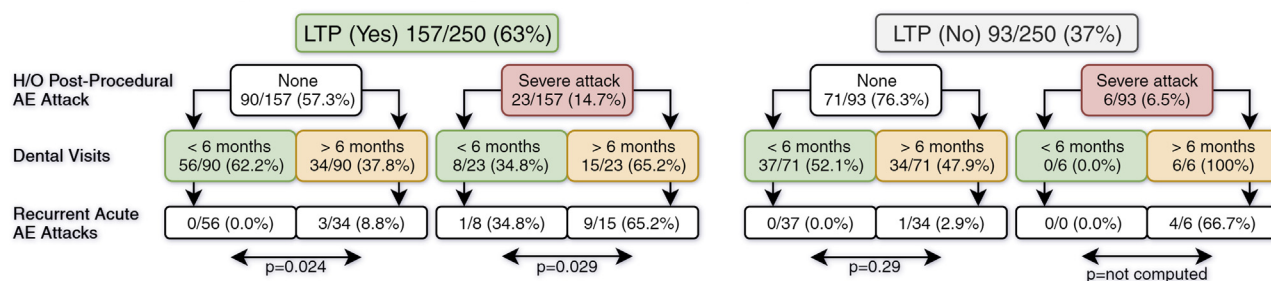


FIGURE 3. Association between long-term prophylaxis (LTP), as a measure of disease severity with routine dental visits, and recurrent postprocedural acute angioedema attacks. A significantly greater number of patients with HAE on LTP had a history of severe AE attack (14.7%) than patients without LTP (6.5%), suggestive of LTP being a surrogate for severity of disease. Stratification by history of severe postprocedural AE attacks and by frequency of dental visits determined that those patients with HAE with severe disease and dental visits >6 months had a proportionally greater number of recurrent AE attacks than similar patients with dental visits <6 months. A history of no AE attacks revealed that a greater number of patients on LTP had more frequent dental visits <6 months, suggesting that a history of severe AE after going to the dentist was more of an influence than being on LTP. There was a significantly lower probability of recurrent procedure-related AE attacks if patients had dental visits <6 months than >6 months. AE, Angioedema; HAE, hereditary angioedema.

important determinant for recurrent AE attacks regardless of teeth brushing frequency. Incidentally, among the patients with HAE with dental visits >6 months, the usage of antibacterial toothpaste was significantly higher by those who had recurrent AE attacks (29.2%) than by those not having such attacks (7.9%) (*P* = .0008) (Figure E3, available in this article's Online Repository at www.jaci-inpractice.org).

Association between long-term prophylaxis and recurrent AE attacks. Given that patients with HAE are started on LTP if they are having more frequent attacks, LTP in this analysis was assumed to be a surrogate marker for disease severity. More than 14% of patients on LTP versus 6.5% of patients not on LTP reported severe postprocedure AE attacks (*P* = .01) (Figure 3). In contrast, 42.7% (67 of 157) of patients

with HAE on LTP versus 23.7% (22 of 93) of patients with HAE not on LTP experienced postprocedural attacks of any severity. Interestingly, a greater number of patients on LTP had dental visits <6 months than patients not on LTP (59.9% vs 47.3%, *P* = .05). This analysis indicates that the patient's history of severe postdental visit AE attacks was a more relevant indicator for less frequent dental visits than being on LTP that during this questionnaire survey was primarily reported to be androgens and intravenous C1-Inh replacement therapy.

Multivariable logistic regression model for recurrent AE attacks. Among all the HAE patient characteristics evaluated, the most relevant factors associated with recurrent AE attacks determined by univariate analyses were the "frequency of routine dental visits," "dental insurance coverage," "on long-term

TABLE III. Multivariate analysis (within-HAE group analysis): significant determinants for recurrent attacks among patients with HAE

Effect	OR (95% CL)	P value
Dental visits (>6 mo vs <6 mo)	3.6 (1.5, 8.7)	.004
Dentures (yes vs no)	6.1 (1.8, 19.9)	.003
On long-term prophylaxis (effect modifier)	3.2 (1.2, 8.8.)	.03

CL, Confidence level; HAE, hereditary angioedema; OR, odds ratio.

HAE prophylaxis,” “severity of previous AE attack,” “presence of dentures,” “use of powered versus manual toothbrush,” “frequency of brushing teeth,” “age,” and “gender.” The “frequency of dental visits” and the “presence of dentures” were determined to be the 2 best factors among the 2-predictor models that provided the lowest AIC values and were therefore included in our multivariable logistic regression model. To further refine the model, being “on long-term HAE prophylaxis” was included as a covariate; its inclusion increased the odds ratio of the association of recurrent AE attacks with dental visit frequency by more than 10%. The odds ratio of recurrent HAE attacks for patients with dental visits >6 months was 3.6 (1.5, 8.7; $P = .004$; for wearing dentures was 6.1 [1.8, 19.9]; $P = .003$) and for being on LTP was 3.2 (1.2, 8.8; $P = .03$) (Table III). The significant association between recurrent AE attacks and wearing dentures requires further investigation to determine causality.

DISCUSSION

In this study, we focused on the important similarities and differences in the dental hygiene practices of patients with HAE compared with matched control (non-HAE) patients. Perceived benefits of preventive dentistry, as is evident from the frequency of dental visits, differed between control and HAE groups and between patients with HAE. The results of this study found that having a history of experiencing recurrent HAE attacks postdental procedures resulted in less frequent routine dental visits that can increase the risk for periodontal disease. The observation that wearing dentures was an effect modifier for the multivariable analysis supports poorer dental hygiene in patients with a history of recurrent postdental procedure AE attacks. This behavior may in turn initiate a perpetuating vicious cycle and thus influence their preference for using oral care products with antibacterial ingredients to reduce their risk for periodontal disease. These findings are consistent with previous studies that have reported concerns about seeking dental treatment among patients with HAE with increased risks of swelling after dental procedures.¹⁶ Interestingly, both subgroups of patients with HAE taking or not taking LTP reported more frequent dental visits <6 months if they had a history of no attacks compared with having severe attacks at the dental office. This suggests that a history of severe postdental AE attacks was more relevant to frequency of visits than being on LTP. At the time of this survey, the LTP therapies used by patients were either androgens or intravenous C1-Inh replacement therapy, the latter of which, in clinical trials, only reduced AE recurrent attacks by 50%.

Among the factors studied, the frequency of routine preventive dental visits was the most significant factor associated with recurrent postprocedural AE attacks. Dental insurance coverage

and access to care is a possible effect modifier, whereas age, gender, race of subjects, and the frequency of oral brushings were not significantly associated with such events. Using stratified analysis between HAE and control groups and within the HAE group, this study determined that despite dental insurance coverage, the patients with HAE had less frequent routine dental visits compared with controls, and such behaviors were significantly associated with having a history of recurrent AE attacks at the dentist.¹⁷

As this study was self-administered by patients with HAE, patients on LTP were considered to have more severe disease. Furthermore, patients on LTP tended to have a history of more severe attacks at the dental office, suggesting that they were a more severe subset of respondents. Interestingly, when LTP was introduced in the final multivariable model to stratify the risk of recurrent procedural AE attacks based on disease severity and frequency of dental visits, it was found to be a significant effect modifier for this analysis.

Collectively, these results provide further understanding of how patients with HAE perceive and practice oral hygiene. Not surprisingly, there is heterogeneity between HAE patient risks for postprocedure swelling episodes that in our study appears to directly influence their frequency of dental visits. Another interesting finding was that patients with HAE with dental visits >6 months reported brushing more frequently with a powered toothbrush in lieu of a manual toothbrush and more frequently endorsed the use of antibacterial toothpaste (Table E4 and Figure E3, available in this article's Online Repository at www.jaci-inpractice.org) that is effective for reducing oral plaque and gingivitis.¹⁸⁻²⁰ These findings suggest that many patients with HAE are not adhering to ADA recommendations compared with matched controls.

The strengths of this study are that it was well powered to achieve meaningful results, involved multiple centers around the United States, and was conducted concurrently on HAE and matched control patients. The absence of intersite variability supports the generalizability of this questionnaire survey. For internal validation of the questionnaire, there were several similar questions included that were asked differently to which participants provided similar responses.

This study was limited by its inability to collect direct information from patients with HAE about their perceptions and attitudes to oral health care to confirm their questionnaire responses and to determine the causality for significant associations between health behaviors and outcomes reported in this study. For example, patients with HAE were not interrogated whether delayed dental visits were related to their fear for recurrent AE attacks or if their preference for antibacterial toothpaste was a compensatory action for delaying dental care. In addition, the questionnaire did not go through a formal validation process. However, this initial questionnaire version will be useful for developing a subsequent validated version. This withstanding, our conclusions are based on the constructs of the health belief model that has been used in similar studies to ascertain important information from patients about their health care beliefs. Finally, as in any questionnaire survey study, there can be selection bias as more motivated patients may be more likely to participate. Having a matched control population that was equally compensated for participation similar to the patients with HAE helped control for this potential limitation.

The results from this study further emphasize the need for clinicians caring for patients with HAE to take a thorough

history regarding their dental hygiene care practices. C1-Inh concentrate as STP has been demonstrated to be efficacious in preventing procedure-related HAE attacks.²¹ Newer prophylactic therapies, recently found to significantly reduce HAE attacks, may ultimately reduce the anxiety and/or concerns by patients with HAE about obtaining routine oral health care and potentially reduce the need for STP. However, until there is further experience with these agents' ability to prevent AE attacks after physical trauma, better efforts should be made to provide those patients with HAE who avoid the dentist with options that may entail changes in oral hygiene care and/or incorporate on-demand versus STP versus LTP treatment approaches to reduce the frequency and severity of attacks experienced at the dentist. Special emphasis should be directed toward educating and motivating patients with HAE on adhering to ADA recommendations for oral hygiene to prevent teeth decay and, subsequently, the need for more invasive traumatic procedures. Surveys of this type should be repeated in the future to determine how current advances in medical management will influence attitudes among patients with HAE regarding oral health care beliefs. Ideally, a prospective randomized controlled trial investigating the association between periodontal/gingival disease and HAE attack frequency related to dental work would best address this gap in knowledge.

REFERENCES

- Forrest A, Milne N, Soon A. Hereditary angioedema: death after a dental extraction. *Aust Dent J* 2017;62:107-10.
- Zanette G, Stellini E, Sivoletta S, Bacci C, Faccio E. Hereditary angioedema and anxiety in oral surgery: a case series report. *Quintessence Int* 2015;46:417-22.
- Gower RG, Busse PJ, Aygoren-Pursun E, Barakat AJ, Caballero T, Davis-Lorton M, et al. Hereditary angioedema caused by c1-esterase inhibitor deficiency: a literature-based analysis and clinical commentary on prophylaxis treatment strategies. *World Allergy Organ J* 2011;4(Suppl):S9-21.
- Nordenfelt P, Dawson S, Wahlgren CF, Lindfors A, Mallbris L, Bjorkander J. Quantifying the burden of disease and perceived health state in patients with hereditary angioedema in Sweden. *Allergy Asthma Proc* 2014;35:185-90.
- Jepsen S, Caton JG, Albandar JM, Bissada NF, Bouchard P, Cortellini P, et al. Periodontal manifestations of systemic diseases and developmental and acquired conditions: consensus report of workgroup 3 of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions. *J Clin Periodontol* 2018;45(Suppl 20):S219-29.
- Morcallo PS, Leonida A, Rossi G, Mingardi M, Martini M, Monguzzi R, et al. Hereditary angioedema in oral surgery: overview of the clinical picture and report of a case. *J Oral Maxillofac Surg* 2010;68:2307-11.
- Roberts A, Shah M, Chapple IL. C-1 esterase inhibitor dysfunction localised to the periodontal tissues: clues to the role of stress in the pathogenesis of chronic periodontitis? *J Clin Periodontol* 2003;30:271-7.
- Bernstein JA. Managing hereditary angioedema patients undergoing otolaryngeal procedures. *Am J Rhinol Allergy* 2013;27:522-7.
- Maeda S, Miyawaki T, Nomura S, Yagi T, Shimada M. Management of oral surgery in patients with hereditary or acquired angioedemas: review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2003;96:540-3.
- Malmstrom HS, Hock JM, Sanford C. Dental management of patients with hereditary angioedema: report of case. *J Am Dent Assoc* 1985;111:957-8.
- Giannobile WV, Braun TM, Caplis AK, Doucette-Stamm L, Duff GW, Kornman KS. Patient stratification for preventive care in dentistry. *J Dent Res* 2013;92:694-701.
- Hollister MC, Anema MG. Health behavior models and oral health: a review. *J Dent Hyg* 2004;78:6.
- Solhi M, Zadeh DS, Seraj B, Zadeh SF. The application of the health belief model in oral health education. *Iran J Public Health* 2010;39:114-9.
- Walker K, Jackson R. The health belief model and determinants of oral hygiene practices and beliefs in preteen children: a pilot study. *Pediatr Dent* 2015;37:40-5.
- Marciano Belisario JS, Jamsek J, Huckvale K, O'Donoghue J, Morrison CP, Car J. Comparison of self-administered survey questionnaire responses collected using mobile apps versus other methods. *Cochrane Database Syst Rev* 2015;7:MR000042.
- Lodi G, Sardella A, Bez C, Demarosi F, Cicardi M, Carrassi A. Dental experience and self-perceived dental care needs of patients with angioedema. *Spec Care Dentist* 2001;21:27-31.
- Lertpimonchai A, Rattanasiri S, Arj-Ong Vallibhakara S, Attia J, Thakkinstian A. The association between oral hygiene and periodontitis: a systematic review and meta-analysis. *Int Dent J* 2017;67:332-43.
- Yaacob M, Worthington HV, Deacon SA, Deery C, Walmsley AD, Robinson PG, et al. Powered versus manual toothbrushing for oral health. *Cochrane Database Syst Rev* 2014;6:CD002281.
- Patil PS, Pujar P, Poornima S, Subbareddy VV. Prevalence of oral malodour and its relationship with oral parameters in Indian children aged 7-15 years. *Eur Arch Paediatr Dent* 2014;15:251-8.
- Swedish Council on Health Technology Assessment (SBU). Systematic Review Summaries. Chronic periodontitis—prevention, diagnosis and treatment: a systematic review. Stockholm, Sweden: SBU; 2004.
- Farkas H, Zotter Z, Csuka D, Szabo E, Nebenfuhrer Z, Temesszentandrási G, et al. Short-term prophylaxis in hereditary angioedema due to deficiency of the C1-inhibitor—a long-term survey. *Allergy* 2012;67:1586-93.

ONLINE REPOSITORY

SITE AND SEVERITY OF ANGIOEDEMA (AE) ATTACKS AFTER DENTAL PROCEDURES

Common sites and severity of AE attacks, as reported by patients who had ever experienced an event after a dental procedure ($n = 89$), revealed that more than 1 swelling location was involved for several patients (Table E1). For example, both face and lips were involved in 29 of 89 (32%) patients reporting an AE attack after any dental procedure. Swellings of the abdomen ($n = 11$; 12%) and extremities ($n = 6$; 7%) were less common. Swelling was perceived to be severe in 29 (33%), moderate in 37 (42%), and mild in 23 (26%) patients. Swellings of the face and lips were more common in patients with hereditary angioedema (HAE) who were highly susceptible to swelling attacks (ie, those who had attacks after every procedure, $n = 29$) and were reported by 23.6% ($n = 21$ of 44) patients with face swelling and by 23.6% (21 of 41) patients with lip swelling. Overall, swelling of the face was significantly reported by a greater percentage of patients with HAE with visits >6 months compared with those with visits <6 months.

ASSOCIATION OF PRODROMES AND POSTPROCEDURE AE ATTACK SEVERITY

HAE prodromes were reported by 29 of 89 (33%) HAE subjects who experienced an AE attack after dental procedures (Table E2). Swelling was reported as moderate to severe by 25 of 29 (86%) HAE subjects experiencing a prodrome, versus 41 of 60 (68%) HAE subjects who did not experience a prodrome ($P = .07$). The perceived severity of swelling was closely associated with the occurrence of HAE prodromal symptoms (relative risk = 1.26 [1.01, 1.58]). The tongue, throat, and/or lips

accounted for 42% and the face and/or mouth accounted for 33% of all swellings associated with prodromes (data not shown).

ASSOCIATION OF RECURRENT POSTPROCEDURAL HAE ATTACKS IN PATIENTS WITH DENTAL VISITS >6 MONTHS AND USE OF ANTIBACTERIAL TOOTHPASTE

A significantly higher percentage of patients with HAE with recurrent postdental procedure AE attacks and dental visits >6 months preferred using antibacterial toothpaste than the patients with HAE not experiencing recurrent postdental procedure AE attacks ($P < .05$) (Figure E3).

ASSOCIATION OF RECURRENT AE ATTACKS WITH SPECIFIC DENTAL PROCEDURES AND DENTAL VISIT FREQUENCY

Recurrent postprocedure AE attacks were reported by 33 patients with HAE. Among them, 73% (24 of 33) usually had dental visits >6 months (Table II). Complicated dental procedures, such as root canal treatment, were needed in more patients with HAE with visits >6 months than for patients with HAE having dental visits <6 months (Table E3). Overall, 48% (16 of 33) of recurrent postprocedure AE attacks were reported during root canal treatment, of which 58% (14 of 24) were experienced by patients with dental visits >6 months versus 22% (2 of 9) among patients with dental visits <6 months ($P = .06$).

APPENDIX

Appendix 1 Questionnaire HAE subjects.pdf

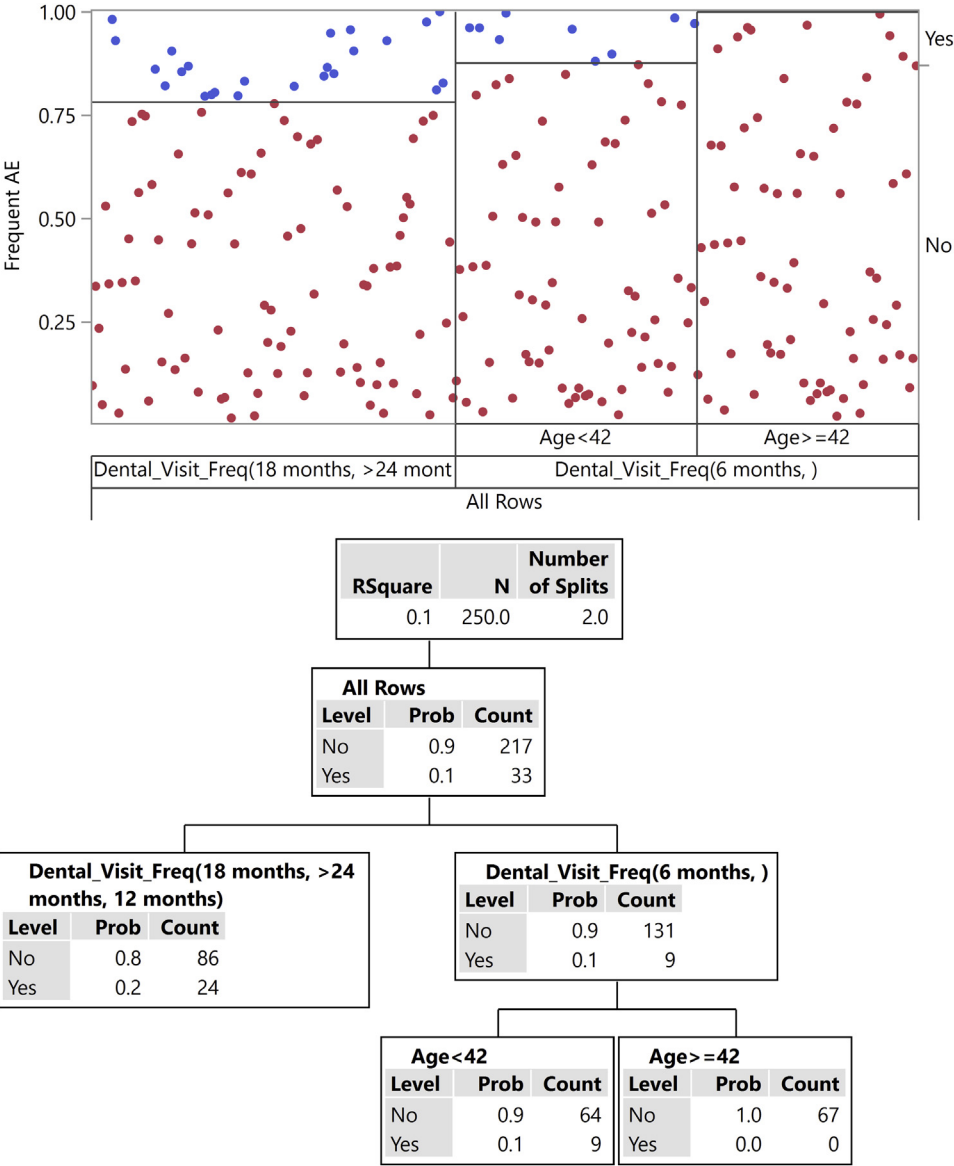
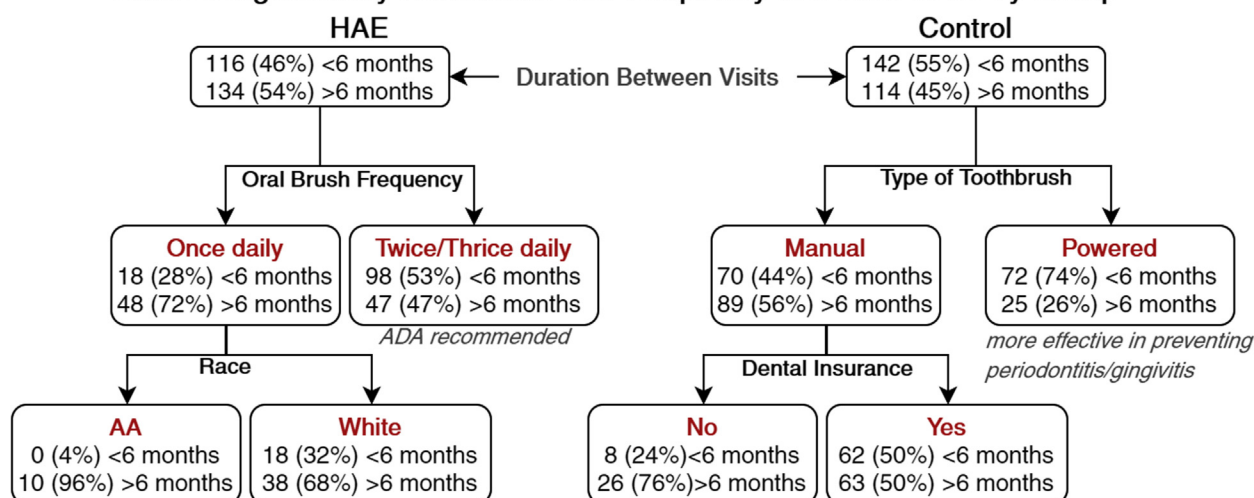


FIGURE E1. Creation of a decision tree to create a heuristic model for frequent angioedema attacks during or immediately after dental procedures. It is based on recursive partitioning of the data for frequent angioedema attacks according to a relationship between the significant factors such as frequency of dental visits, age, and response values (yes/no) of the angioedema attacks. This heuristic approach was taken to determine the optimum frequency of preventive dental visits for HAE subjects to prevent frequent procedure-related angioedema attacks. Each of the splits is chosen to maximize the difference in the responses between the 2 nodes of the split. *AE*, Angioedema; *HAE*, hereditary angioedema.

Factors Significantly Associated with Frequency of Dental Visits by Group



Frequency of Dental Visits

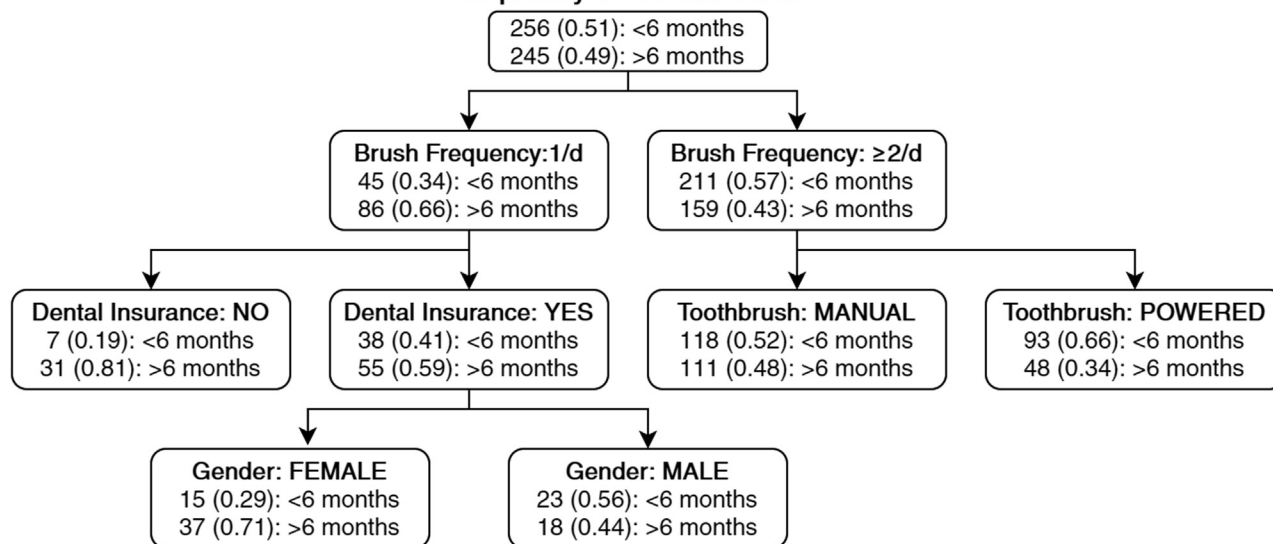


FIGURE E2. Tree analysis showing major factors associated with frequency of dental visits between HAE and control groups (top panel) and both groups combined (bottom panel); numbers indicate count probability. Routine oral care practices (ie, oral brushing frequency) and race of patients were most significantly associated with the frequency of dental visits in patients with HAE; similarly, oral care practices (ie, use of powered toothbrush) and dental insurance were the most significant determinants of frequency of dental visits in control patients. Approximately 46% ($n = 116$ of 250) of the HAE vs 55% ($n = 142$ of 256) of control patients had regular dental visits <6 months. Among patients with HAE, 53% (98 of 145) who brushed their teeth twice daily, as recommended by American Dental Association (ADA), had regular dental visits every 6 months. In contrast, only 28% (18 of 66) of HAE subjects who brushed their teeth only once daily had regular dental visits. Among the controls, 74% ($n = 72$ of 97) of powered toothbrush users vs 44% ($n = 70$ of 159) of manual toothbrush users had regular dental visits. In this subgroup, approximately 50% ($n = 62$ of 125) those with dental insurance vs 24% ($n = 8$ of 34) of those without dental insurance had regular dental visits. The association between use of powered toothbrush and frequency of dentist visits was significant for the control group ($P < .0001$) but not the HAE group ($P = .73$). HAE, Hereditary angioedema.

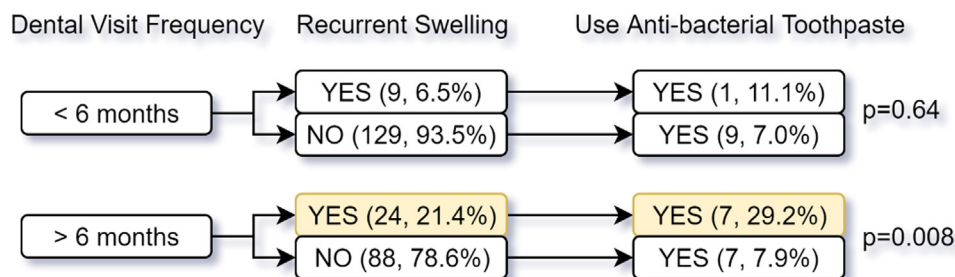


FIGURE E3. Association of antibacterial toothpaste usage with recurrent procedure-related angioedema attacks. Patients with HAE with dental visits >6 months were more likely to experience recurrent procedure-related angioedema attacks (24 of 112; 21%) and use antibacterial toothpaste. This association was not seen for patients with HAE with more frequent dental visits <6 months. *HAE*, Hereditary angioedema.

TABLE E1. Associations between severity of procedure-related angioedema attacks at specific anatomical sites* and frequency of dental visits

Site (n)	Severity (n)	Dental visit frequency		P value (χ^2 analysis)
		<6 mo (n/row-total, row%)	>6 mo (n/row-total, row%)	
Mouth (57)	Mild (16)	10/16 (62.50%)	6/16 (37.50%)	.06
	Moderate (23)	14/23 (60.87%)	9/23 (39.13%)	
	Severe (18)	5/18 (27.78%)	13/18 (72.22%)	
Face (44)	Mild (5)	1/5 (20%)	4/5 (80%)	.15
	Moderate (18)	10/18 (55.56%)	8 (44.44%)	
	Severe (21)	6/21 (28.57%)	15/21 (71.43%)	
Tongue (13)	Mild (1)	1/0 (100%)	0/1 (0.0%)	.29
	Moderate (5)	3/5 (60%)	2/5 (40%)	
	Severe (7)	2/7 (28.57%)	5/7 (71.43%)	
Throat (26)	Mild (3)	3/3 (100%)	0/3 (0%)	.002
	Moderate (8)	6/8 (75%)	2/8 (25%)	
	Severe (15)	2/15 (13.33%)	13/15 (86.67%)	
Lips (41)	Mild (4)	3/4 (75%)	1/4 (25%)	.03
	Moderate (16)	10/16 (62.5%)	6/16 (37.5%)	
	Severe (21)	5/21 (23.81%)	16/21 (76.19%)	
Abdomen (11)	Mild (1)	1/1 (100%)	0/1 (0%)	.27
	Moderate (6)	4/6 (66.67%)	2/6 (33.33%)	
	Severe (4)	1/4 (25%)	3/4 (75%)	
Extremities (6)	Mild (0)	0 (0%)	0 (0%)	Row sum zero. No statistics computed
	Moderate (3)	2/3 (66.67%)	1/3 (33.33%)	
	Severe (3)	2/3 (66.67%)	1/3 (33.33%)	
Other (4)	Mild (1)	1/1 (100%)	0/1 (0%)	.37
	Moderate (1)	0/1 (0%)	1/1 (100%)	
	Severe (2)	1/2 (50%)	1/2 (50%)	

Bold values indicate statistically significant differences in location of hereditary angioedema related attacks and dental visit frequency >6 months.

*Several subjects reported multiple locations.

TABLE E2. Association between HAE prodromes and consequent severity of AE attacks

Prodrome	Severity of AE attack		Total
	Severe-moderate	Mild	
Yes	25 (86.2%)	4 (13.8%)	29
No	41 (68.3%)	19 (31.7%)	60
Total	66	23	89

RR (95% CL) = 1.26 (1.01, 1.58); $P = .07$.

AE, Angioedema; CL, confidence level; HAE, hereditary angioedema; RR, relative risk.

TABLE E3. Association of recurrent AE attacks with specific dental procedures with frequency of dental visits in patients with HAE*

Dental procedures	Total	<6 mo	>6 mo	<i>P</i> value
Dental cleaning	15/33 (45%)	5/9 (55.6%)	10/24 (41.7%)	.48
Cavity filling	22/33 (67%)	7/9 (77.8%)	15/24 (62.5%)	.41
Root canal	16/33 (48%)	2/9 (22.2%)	14/24 (58.3%)	.06
Crown/bridge	13/33 (39%)	2/9 (22.2%)	11/24 (45.8%)	.21

AE, Angioedema; HAE, hereditary angioedema.

*The sum of all numerators (in the "Total" column) does not equal the denominator (33) as several patients reported having more than 1 procedure.

TABLE E4. Dental visit frequency by type of toothbrush usage

Dental visit frequency	Type of toothbrush		Total
	Manual	Electric	
Beyond 6 mo	79	29	108
Row %	73.2%	26.9%	
Within 6 mo	85	51	136
Row %	62.5%	37.5%	
Total	164	80	244

Missing = 3; P value = .07.

Dental Hygiene Practices: Questionnaire Survey

FOR HAE SUBJECTS

Please complete the survey below.

Upon completion of the survey you will receive a complimentary gift card from your HAE specialist

Thank you!

Demography

Time _____

Longitude _____

gift code _____

[idn_hae] PC[phy_code2] _____

Location (City) _____

State

- ☐ ALABAMA ☐ ALASKA
☐ ARIZONA ☐ ARKANSAS
☐ CALIFORNIA ☐ COLORADO
☐ CONNECTICUT ☐ DELAWARE
☐ FLORIDA ☐ GEORGIA
☐ GUAM ☐ HAWAII ☐ IDAHO
☐ ILLINOIS ☐ INDIANA
☐ IOWA ☐ KANSAS ☐ KENTUCKY
☐ LOUISIANA ☐ MAINE
☐ MARYLAND ☐ MASSACHUSETTS
☐ MICHIGAN ☐ MINNESOTA
☐ MISSISSIPPI ☐ MISSOURI
☐ MONTANA ☐ NEBRASKA
☐ NEVADA ☐ NEW HAMPSHIRE
☐ NEW JERSEY ☐ NEW MEXICO
☐ NEW YORK ☐ NORTH CAROLINA
☐ NORTH DAKOTA ☐ OHIO
☐ OKLAHOMA ☐ OREGON
☐ PENNSYLVANIA ☐ PUERTO RICO
☐ RHODE ISLAND ☐ SOUTH CAROLINA
☐ SOUTH DAKOTA ☐ TENNESSEE
☐ TEXAS ☐ UTAH ☐ VERMONT
☐ VIRGINIA ☐ WASHINGTON
☐ WEST VIRGINIA ☐ WISCONSIN
☐ WYOMING ☐ VIRGIN ISLANDS

Zip Code

(must answer this question)

Please select your treating HAE specialist

- ☐ Aleena Banerji
☐ Bill Lumry
☐ Bruce Zuraw
☐ Henry Li
☐ Jonathan Bernstein
☐ Josh Jacobs
☐ Marc Riedl
☐ Mark Davis-Lorton
☐ Paula Busse
☐ Sandra Christiansen
☐ Tim Craig
☐ SUMMIT
(must answer this question)

[treating_phys]

Year of Birth

(must answer this question)

Gender

- ☐ Female
☐ Male

Race (check best answer)

- ☐ White
☐ Black / African-American
☐ American Indian / Alaskan Native
☐ Other

Ethnicity (check best answer)

- ☐ Hispanic or Latino
- ☐ Non-Hispanic or Latino

Type of Angioedema (check best answer)

- ☐ Hereditary type 1
- ☐ Hereditary type 2

Prophylactic Treatment for Angioedema

On Prophylactic Medication?

☐ Yes ☐ No
(must answer this question)

Select Prophylactic Medication(s) (check all that apply)
(must answer this question)

- ☐ Danazol/Androgens
☐ Tranexamic acid
☐ C1-INH replacement
☐ Other
☐ (not sure)

Danazol Dose (total dose, mg/day)
(must answer this question)

☐ 50mg ☐ 100mg ☐ 150mg ☐ 200mg ☐ 300mg ☐ 400mg ☐ Other ☐ (not sure)

Tranexamic Acid Dose (grams / day)
(select best answer from the list)
(must answer this question)

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ more than 4 ☐ not sure

C1-Inhibitor medication
(check all that apply)
(must answer this question)

- ☐ CINRYZE®
☐ BERINERT®
☐ Other
☐ (not sure)

Cinryze Dose (Units, every 3 or 4 days)
(check best answer)

☐ 1000 ☐ 2000 ☐ 3000 ☐ 4000 ☐ more than 4000 ☐ Not sure

Berinernt Dose (units)

☐ less than 1500 ☐ 1500-2000 ☐ 2001-2500 ☐ 2501-3000 ☐ 3001-3500 ☐ more than 3500
☐ Not sure

On-Demand Treatment for Angioedema

On-Demand Treatment for Angioedema

(check all that apply)

(must answer this question)

- ☐ FIRAZYR® (icatibant injection)
- ☐ BERINERT® (C1 Esterase Inhibitor)
- ☐ RUCONEST® (C1 esterase inhibitor [recombinant])
- ☐ KALBITOR® (ecallantide)
- ☐ Other

Dental Care Access

How long ago was your last visit to the dentist?

(check best answer)

(must answer this question)

- ☐ less than 6 months
- ☐ 6-12 months
- ☐ 13-18 months
- ☐ more than 18 months
- ☐ Never

How often do you see your dentist for a check-up/cleaning?

(must answer this question)

- ☐ 6 months
- ☐ 12 months
- ☐ 18 months
- ☐ more than 24 months

Do you have dental insurance?

(must answer this question)

- ☐ Yes
- ☐ No

Does having dental insurance or not having dental insurance influence you going to see a dentist?

(must answer this question)

- ☐ Yes
- ☐ No

Have you avoided dental check-ups/cleanings or procedures because of your angioedema?

(must answer this question)

- ☐ Yes
- ☐ No

If you have avoided dental care because of your HAE, why?

(check all that apply)

(must answer this question)

- ☐ Concern about swelling attacks
- ☐ Insurance/cost
- ☐ Other

If other, then please specify:

Is your dental professional aware of your angioedema condition?

(must answer this question)

- ☐ Yes
- ☐ No

Dental Procedure-Induced Angioedema Attack

Have you ever had a swelling (angioedema) attack immediately after a dental procedure?
(must answer this question)

- ☐ Yes
☐ No

If yes, where on your body was the swelling located?
(check all that apply)
(must answer this question)

- ☐ Mouth
☐ Face
☐ Tongue
☐ Throat
☐ Lips
☐ Abdomen
☐ Extremities
☐ Other

What was the degree of swelling severity
(check best answer)
(must answer this question)

- ☐ Mild
☐ Moderate
☐ Severe

Was there any prodrome (funny feeling or symptom) prior to the attack occurring?
(must answer this question)

- ☐ Yes
☐ No

If Yes, describe the prodrome:

Was the swelling attack treated?
(must answer this question)

- ☐ Yes
☐ No

What was used to treat the attack?
(check all that apply)

- ☐ FIRAZYR® (icatibant injection)
☐ BERINERT® (C1 Esterase Inhibitor)
☐ CINRYZE® (C1 esterase inhibitor)
☐ KALBITOR® (ecallantide)
☐ RUCONEST® (recombinant C1INH)
☐ Other
☐ Not sure

Was the treatment successful?
(must answer this question)

- ☐ Yes
☐ No
☐ Partially

If not or partially successful, then was a second treatment required?
(must answer this question)

- ☐ Yes
☐ No

How long did it take for the attack to resolve? (Select one)

- ☐ 30 minutes or less ☐ 1 hour ☐ 2 hours ☐ 3 hours ☐ 4 hours ☐ 6 hours ☐ 8 hours
☐ 10 hours ☐ 12 hours ☐ 18 hours ☐ 24 hours ☐ more than 24 hours ☐ Do not remember

Do you swell after every dental procedure?
(must answer this question)

- ☐ Yes
☐ No

Have you refused a dental procedure (such as a filling, crown) because of your angioedema?

- ☐ Yes
☐ No

Short-Term Prophylaxis

If you go to a dentist for a procedure, do you use preventative (short term prophylactic treatment) angioedema therapy 1-2 hours prior?

- ☐ Yes
☐ No

If Yes, for which procedures?
(check all that apply)

- ☐ Dental cleaning
☐ Cavity filling
☐ Root canal
☐ Crown or Bridge
☐ Other

If Yes, which treatment is used?
(check all that apply)

- ☐ FIRAZYR® (icatibant injection)
☐ BERINERT® (C1 Esterase Inhibitor)
☐ CINRYZE® (C1 esterase inhibitor)
☐ KALBITOR® (ecallantide)
☐ RUCONEST® (recombinant C1INH)
☐ Other

If 'other', then please specify:

Did you experience an angioedema attack even after receiving the preventive medication?

- ☐ Yes
☐ No

Home Oral Hygiene Routine

I brush my teeth
(check best answer)

- ☐ Never
- ☐ Once a day
- ☐ Twice a day
- ☐ After each meal
- ☐ Other

I brush my teeth using (check best answer)

- ☐ A manual tooth brush
- ☐ An electric toothbrush
- ☐ Other

I brush my teeth with:
(check all that apply)

- ☐ A fluoride containing tooth paste
- ☐ An anti-bacterial toothpaste
- ☐ A teeth whitening toothpaste
- ☐ Herbal and natural toothpaste
- ☐ Other

I floss my teeth:
(check best answer)

- ☐ Never
- ☐ Once a day
- ☐ Twice a day
- ☐ After each meal
- ☐ Other

I have dentures:
(check best answer)

- ☐ Yes
- ☐ No

If Yes, then type of dentures:
(check all that apply)

- ☐ Partial Upper
- ☐ Partial Lower
- ☐ Complete

Medical History: Do you have the following medical conditions?

High blood pressure (hypertension)?

- ☐ Yes
☐ No
(must answer this question)

High blood sugar (diabetes mellitus)?

- ☐ Yes
☐ No
(must answer this question)

High blood cholesterol (hypercholesterolemia)?

- ☐ Yes
☐ No
(must answer this question)

Runny Nose (Rhinitis: Allergic or Non-Allergic)

- ☐ Yes
☐ No
(must answer this question)

Asthma

- ☐ Yes
☐ No
(must answer this question)

Medications: Do you take any of the following medications for any medical condition?

Nasal Steroids (Inhaled, e.g., for runny nose/rhinitis)

- ☐ Yes
☐ No
(must answer this question)

Corticosteroids (Oral or Inhaled, e.g., for asthma)

- ☐ Yes
☐ No
(must answer this question)

Supplementary Oxygen (e.g., for COPD)

- ☐ Yes
☐ No
(must answer this question)

Phenytoin (Dilantin(R))

- ☐ Yes
☐ No
(must answer this question)

Immune suppressing drugs

- ☐ Yes
☐ No
(must answer this question)

High blood pressure medications (such as nifedipine, amlodipine, verapamil, diltiazem)

- ☐ Yes
☐ No
(must answer this question)

Regular use of sweetened medications such as cough syrups, antacids, anti-fungal, vitamins

- ☐ Yes
☐ No
(must answer this question)

End of Questionnaire

This is the end of the survey. Click 'Submit' to save and transmit the responses. Your unique identifier code can be viewed on the next page. Save this code. This code will only track your responses in this survey, but not any of your personal information.