COHORT STUDY

Very High Salivary *Streptococcus Mutans* Predicts Caries Progression in Young Children

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Abstract: ***Purpose:*** *Culturing mutans streptococci (MS) from children's saliva has high utility in caries risk assessment. The purpose of this retrospective cohort study was to examine its ability in predicting caries progression and determine sensitivity, specificity, and likelihood ratios of a very high [“too numerous to count (TNTC) MS test result.* ***Methods:*** *200 preschoolers (3.3±1.2 years, 50 percent no recoverable MS, 50 percent TNTC MS at first dental visit) were followed for five or more years. Caries experience of both groups was compared to identify predictors of caries presence and its progression.* ***Results:*** *Controlling for demographic, oral health, and dental visit factors, TNTC preschoolers had both greater presence and extent of caries at the first dental visit (adjusted odds ratio [aOR] 8.0, 95 percent confidence interval [CI] 2.5 to 25.5) and caries progression at five or more years (aOR 6.0, 95 percent CI 2.4 to 15.0). Fewer TNTC preschoolers remained caries free over five years or longer (13 percent versus 77 percent for no MS). Overall, sensitivities and specificities exceeded 75 percent.* ***Conclusions:*** *Despite engagement in preventive dental care, children with TNTC MS were six times more likely to experience cavity increments than preschoolers with no recoverable MS at first visit.* *(Pediatr Dent 2016;38(4):325-30) Received February 23, 2016 / Last Revision May 1, 2016 / Accepted May 16, 2016*

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Childhood caries in the United States remains prevalent, consequential, and disparately distributed by race and income[1-3] yet significantly preventable.[4,5] In an era of increasing interdisciplinary collaboration, identifying young children at risk for caries occurrence and progression is of interest to both dental and pediatric primary care providers.[6] Both the American Academy of Pediatric Dentistry[7] and American Academy of Pediatrics[8] promote early screening, counseling, fluoride application, and dental care for at-risk young children, but the United States Preventive Services Task Force finds “insufficient evidence” of “routine screening exams for dental caries by primary care clinicians.”[9,10] Dental and pediatric medical providers would benefit from an objective test that identifies children at high risk for caries initiation and progression.

The literature on pediatric caries prediction is robust but not definitive, and longitudinal incidence studies are fewer than cross-sectional prevalence studies.[11] Caries prediction models generally include microbiological, dietary, behavioral, social, and environmental factors reflective of the disease's multifactorial etiology and correlates.[12] Given that cariogenesis involves an essential microbiologic component, many risk models include assays of salivary levels of cariogenic organisms. Multiple acidogenic and aciduric bacteria contribute to caries pathogenesis, raising question about which organisms to assay, yet mutans streptococci (**MS**) are pathognomonic for early childhood caries.[13] Nonetheless, evidence for the value of MS testing for caries prediction is equivocal[14-16] and additional investigation is warranted.

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Our prior work in children younger than three years old[17] determined that salivary MS culture may be more effective, simpler, and less time consuming than risk assessments utilizing the American Academy of Pediatric Dentistry's Caries Risk Assessment Tool. The purposes of this study were to: consider the value of salivary mutans streptococci cultures in identifying children six years old or younger at their first dental visit for caries occurrence and progression over five or more years; examine caries increment over time in a cohort of young children identified with no recoverable salivary MS (zero MS group) compared to children with very high levels of salivary MS (“too numerous to count [**TNTC**]” group) at their initial assessment and identify factors associated with caries increment; and determine the clinical accuracy and utility of MS testing for anticipating caries increments over time.

Methods

Setting, subject identification, and eligibility. With approval from the Institutional Review Board of Columbia University Medical Center, New York, N.Y., USA, we conducted a retrospective chart review comparing caries progression over five or more years in young children with zero and TNTC oral MS levels who were followed at a single private pediatric dental practice: the Children's Dental Associates of New London County Connecticut, P.C. (**CDA**), New London, Conn., USA. CDA is a single-specialty pediatric dental group practice that serves a socioeconomically mixed population in a predominantly fluoridated area where children requiring fluoride supplementation receive prescriptions for recommended supplements. At the time of the study, the practice involved seven American Board of Pediatric Dentistry (**ABPD**)- certified pediatric dentists serving over 17,000 unique children annually. The practice has served as a research site to investigate caries risk assessment since the mid-1980s.[18,19]

Saliva of all new patients at CDA is routinely cultured for MS as a component of the practice's caries risk assessment and management protocols. Hygienists obtained a sample of saliva by depressing a sterile tongue blade onto the dorsal surface of the child's tongue and then pressing the tongue blade onto an agar plate containing media selective for MS (modified Gold's medium composed of a mitis salivarius agar base, 20 percent sucrose, and 0.2 U/ml bacitracin with the addition of sorbitol and kanamycin sulfate and bacitracin[20]). Plates are incubated for two days at 35 to 37 degrees Celsius in a tied-off plastic bag inflated with expired air to create a partially anaerobic environment. Using a visual template, intensity of bacterial growth on each plate is read as colony forming units (**CFU**) equivalents by a single designated hygienist during the study period and recorded as: zero (no apparent growth); low (one to nine CFU); moderate (10 to 99 CFU); high (100 to 100,000 CFU); and TNTC (greater than 100,000 CFU). MS findings are recorded in the Dentech Enterprise practice management system (Henry Schein Inc., Melville, N.Y., USA).

Table 1. CHARACTERISTICS OF THE SAMPLE AT THE INITIAL DENTAL VISIT AND AT THE FIVE-YEAR FOLLOW-UP OR LATER*

	Total sample (N=200)		**Zero MS (N=100)**		**Very high MS (N=100)**		***P*-value**
Initial dental visit							
	Mean±(SD)		**Mean±(SD)**		**Mean±(SD)**		
Child age (ys)†	3.3±1.2		3.3±1.2		3.3±1.2		NS
Maternal age (ys)†	29.6±5.5		30.6±5.0		28.6±5.9		0.008
No. of carious teeth at initial visit†	1.6±2.9		0.2±0.8		2.9±3.5		<0.001
Oral hygiene score at initial visit†	3.7±2.8		3.7±2.7		3.7±2.9		NS
	N	%	N	%	N	%	
Gender (female)‡	105	52.5	54	54.0	51	51.0	NS
Presence of caries at initial visit‡							
Yes	73	36.5	11	11.0	62	62.0	<0.001
No	127	63.5	89	89.0	38	38.0	
Mother's marital status‡							
Single	22	11.0	5	5.0	17	17.0	0.02
Married	171	85.5	92	92.0	79	79.0	
Separated/divorced	7	3.5	3	3.0	4	4.0	
Health insurance type‡							
Medicaid/CHIP	26	13.0	3	3.0	23	23.0	<0.001
Private insurance	164	82.0	94	94.0	70	70.0	
No dental insurance	9	4.5	3	3.0	6	6.0	
Missing	1	0.5	0	0.0	1	1.0	
At ≥5 ys of dental follow-up							
	Mean±(SD)		**Mean±(SD)**		**Mean±(SD)**		
Follow-up (ys)†	7.9±1.7		8.7±1.6		7.0±1.3		<0.001
No. of visits over follow-up period†	13.5±3.9		15.4±3.7		11.7±3.2		<0.001
Visits/year over follow-up period†	1.7±0.3		1.8±0.3		1.7±0.3		0.01
Delta dft over follow-up period†	2.9±4.4		0.6±1.4		5.2±5.1		<0.001
Mean oral hygiene score over follow-up†	4.2±1.4		3.8±1.2		4.5±1.5		0.002
	N	%	N	%	N	%	
Caries increment over study duration‡							
Yes	97	48.5	20	20.0	77	77.0	<0.001
No	103	51.5	80	80.0	23	23.0	
Caries free at end of study period‡							
Yes	90	45.0	77	77.0	13	13.0	<0.001
No	110	55.0	23	23.0	87	87.0	

* MS=mutans streptococci; CHIP=Children's Health Insurance Program; dft=decayed, filled primary teeth; NS=not statistically different.
† Student's *t*-test. ‡ Chi-square test.

The practice management system was queried to identify the first 100 children with zero MS levels and the first 100 with TNTC MS levels that met the inclusion criteria of being equal to or younger than six years old at the time of their first dental visit, having ongoing follow-up at CDA for at least five years, not taking an antibiotic or xerostomic medication at the time of the initial visit, and not having a chronic health condition.

All children are provided with comprehensive dental care, including semiannual prevention visits, diet counseling, topical and systemic fluoride supplementation, restorative dentistry, and routine placement of sealants. While all CDA patients are engaged in a recall system, the intensity and content of caries counseling is tailored to assessed level of risk based, in part, on findings of MS culturing as well as past child and familial caries experience and clinical findings.

Clinical charts for all 200 subjects were retrieved and reviewed by one author (SU) to validate inclusion criteria and extract information on patient characteristics at the initial visit, including child age, maternal age and marital status, numbers of carious teeth, dental plaque score (using the simplified oral hygiene index[21]), and type of insurance (uninsured, private, or public [Medicaid or Children's Health Insurance Program]). Data were also extracted from records of preventive visits, but not other types of dental visits, on caries increment and oral hygiene scores. Public insurance coverage served as a proxy for low-income status. Because all children had fluoride exposure either through community water systems or prescription supplementation, fluoridation status was not included in analyses. The presence of dental caries (decayed and filled due to caries) was clinically and radiographically assessed and charted by CDA's pediatric dentists.

Data were entered into a Microsoft Office Excel database (Microsoft Corp., Redmond, Wash., USA) and checked for missing values and data entry errors. Data were stored on a password-protected computer that was backed up daily. Statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, N.C., USA). Demographic characteristics of children with zero and TNTC MS levels were compared using chi-square analyses and student's *t*-tests. Variables that achieved statistical significance ($P<0.05$) in bivariate analyses were entered into simple and multivariate logistic regression models to identify factors that independently predicted caries increment over time (the dependent variable). Diagnostic test

Table 2. UNADJUSTED AND ADJUSTED ODDS RATIOS FOR CARIES INCREMENT AT THE FIVE-YEAR DENTAL FOLLOW-UP OR LATER*

Variable	OR	95% CI	aOR	95% CI
Maternal age	0.95	0.90-1.00	0.99	0.93-1.07
Maternal marital status	0.35	0.15-0.81	0.47	0.15-1.47
Health insurance type	0.61	0.35-1.05	0.75	0.38-1.46
TNTC mutans streptococci at initial dental visit	13.39	6.81-26.33	6.04	2.43-15.03
Presence of caries at initial dental visit	11.23	5.51-22.86	8.0	2.51-25.53
No. of carious teeth at initial dental visit	1.48	1.25-1.76	0.89	0.73-1.09
Mean oral health score	1.38	1.11-1.73	1.10	0.84-1.45
No. of preventive dental visits over follow-up period	0.81	0.75-0.88	0.85	0.72-1.00
Years of follow-up	0.68	0.56-0.81	1.25	0.84-1.84

* OR=odds ratio; aOR=adjusted odds ratio; CI=confidence interval; TNTC=too numerous to count; Adjustments were made for presence of caries at baseline, maternal age and marital status, health insurance type, number of preventive dental visits, and mean oral hygiene score over the follow-up period.

Table 3. TEST PROPERTIES OF SALIVARY MUTANS STREPTOCOCCI AT BASELINE DENTAL ASSESSMENT*

Outcome based on MS status	Sensitivity (%)	Specificity (%)	Discriminant ability	Predictive value		Likelihood ratio (LR)	
				PPV	NPV	LR+	LR-
Presence of caries at baseline	84.9	70.1	77.5	62	89	2.8	0.22
Presence of caries at ≥5 ys	79.0	85.6	82.3	87	77	5.5	0.25
Caries increment at ≥5 ys with or without caries at baseline	79.4	77.7	78.6	77	80	3.6	0.27
Caries increment at ≥5 ys for those with no caries at baseline†	67.6	85.6	76.6	65.7	86.5	4.7	0.38

* MS=mutans streptococci; PPV=positive predictive value; NPV=negative predictive value.

† N=127 caries-free children at baseline (too numerous to count MS=38, 0 MS=89); discriminant ability=average of sensitivity and specificity.

properties (sensitivity and specificity and likelihood ratios) were calculated to examine the predictive ability of a TNTC salivary MS test finding to detect the presence of caries at baseline, caries increment at equal to or greater than five years, presence of caries at equal to or greater than five years, and caries increment for those who were caries free at the first dental visit.

Results

Of 17,157 unique patient records with MS findings in the Dentech practice management list, 8,230 (48 percent) had zero MS and 808 (4.7 percent) had TNTC MS. The first 100 children with zero counts and the first 100 children with TNTC MS who met all inclusion criteria were selected for further analysis.

Table 1 presents the characteristics of the sample at the initial dental visit and at the end of the follow-up period. At the initial visit, there were no differences between the two groups regarding child age, gender, or initial oral hygiene score. Mothers of children with TNTC MS levels were on average two years younger than mothers of children with zero MS levels (P=0.008), and fewer were married (P=0.02). The prevalence of dental caries at the time of the first dental visit in the overall sample was 36.5 percent.

Children with TNTC MS at the initial presentation had greater cavity experience than children with zero MS (62 percent and 11 percent, respectively; P<0.001) and more extensive cavity experience (2.9 and 0.2 cavitated teeth, on average, respectively; P<0.001). More children with TNTC MS at initial presentation were enrolled in Medicaid or CHIP compared to children with zero mutans levels (23 percent and three percent, respectively; P<0.001).

At five or more years of follow-up, children with TNTC MS levels were noted to have had fewer total prevention visits (11.7 versus 15.4; P<0.001) and shorter retention in care (7.0 years versus 8.7 years; P<0.001). While there was a statistical difference in the numbers of prevention visits, these were likely not clinically impactful (1.7 prevention visits per year and 1.8 such visits, respectively; P=0.01). A greater percentage of children with TNTC MS counts at the initial visit had caries increment compared to those with zero MS (77 percent versus 20 percent; P<0.001). While 38 percent of children with TNTC MS levels were caries-free at baseline, only 13 percent remained caries free by the end of the study. Among children with zero MS levels, 89 percent were caries-free at baseline and 77 percent remained caries free. Caries increments on average were 8.6 times greater for children with TNTC MS levels than for children with zero MS (5.2 teeth versus 0.6 teeth; P<0.001). Averaging oral hygiene scores over multiple visits, TNTC MS children demonstrated poorer oral hygiene than did zero MS children (4.5 versus 3.2; P=0.002).

Table 2 presents unadjusted and adjusted results of the logistic regression analysis modeling caries increment at the end of the follow-up period. Adjusting for presence of caries at baseline, maternal age and marital status, health insurance type, number of preventive dental visits over the follow-up period, and mean oral hygiene score, two factors independently predicted caries increment: (1) TNTC MS; and (2) presence of caries at the initial dental visit. Children with cavities present at the initial dental visit were eight times more likely to experience an increment in decayed teeth compared to caries-free children at the initial dental visit (aOR equals 8.0, 95 percent confidence interval [**CI**] equals 2.5 to 25.5). Children with TNTC MS levels were six times more likely (aOR equals 6.0, 95 percent CI equals 2.4 to 15.0) to experience cavity increment compared to those with zero MS at the initial dental exam. Notably, income level, as identified by the surrogate Medicaid/CHIP coverage, was not predictive of cavity increment when other variables were considered.

Table 3 presents the test properties of MS culturing for this sample of young children. Sensitivity ranged between 67.6 to 84.9 percent and was highest for detecting caries at baseline. Specificity ranged between 70.1 and 85.6 percent, with the highest specificity noted for predicting caries and/or increment at equal to or greater than five years in children who had been caries free at baseline. Likelihood ratios were modest overall, with the greatest positive likelihood (5.5) for predicting the presence of caries at equal to or greater than five years and a negative likelihood ratio (0.22) for caries detection at baseline. The likelihood of the presence of dental caries at baseline was 78 percent lower for a child with zero MS compared to those with a TNTC MS test. Despite ongoing engagement in dental care, the likelihood of caries at equal to or greater than five years after the initial dental visit was 5.5 times higher for a child with a TNTC MS test at baseline compared to those with a negative test (zero MS).

Discussion

Important findings of this study are that: (1) salivary culture of MS in children six years old and younger is a clinically useful tool for the identification of those at high risk for caries occurrence and progression, including children who do not yet display visual evidence of cavities; (2) TNTC MS levels, compared to unrecoverable or zero MS levels, are significantly predictive of cavity increments over time; (3) early visual presence of cavities is significantly predictive of cavity increments over time; and (4) a young child's status as a Medicaid or CHIP beneficiary (reflecting poverty or low-income status), is not independently predictive of cavity occurrence or progression.

While these clinical findings and reported test characteristics are clinically useful for children demonstrating very low and very high MS levels, it is important to note that approximately half of the children in the practice had MS levels that were intermediary to these extremes at the initial visit. The implications of these intermediary MS levels at the first dental visit remain unexplored, and future research is needed to examine their clinical usefulness.

Our previous cross-sectional work comparing four methods of caries risk assessment determined that salivary MS culture alone outperformed the American Academy of Pediatric Dentistry's Caries Risk Assessment Tool (**CAT**) and variations of the CAT for accuracy (sensitivity and specificity) and clinical utility (predictive values).[17] Of greater clinical value to dental and pediatric providers is the finding of the current longitudinal study that TNTC MS levels are predictive of high risk for disease progression over time, even in children who do not yet clinically demonstrate dental cavities.

In addition to informing dental care, these findings also inform primary care pediatrics as it seeks to implement recommendations for medical practitioners that support an active role in oral health supervision through caries risk assessment, anticipatory guidance, caries prevention counseling, application of topical fluorides, and referral to dentists. MS culturing appears to be a valid and reliable caries risk predictive approach that is clinically acceptable to young children and their families and is quicker, easier, and, therefore, less expensive and more efficient to execute than caries risk tools that require extensive parent interviewing.[17] While a dental visit for each child by the age of one year is the recommended standard of care, only a minority of children zero to two years old actually receives preventive dental health services,[22] with minority and poor children least likely to utilize dental care. Our findings suggest that MS culturing in non-dental settings may be useful in assessing the risk of young children for selective timely referral to dental services.

This study's findings must be interpreted within the context of other studies examining caries incidence or its progression in young children over time.[12,16,23-29] Of nine cohort studies, four[12,16,23,24] were conducted in the United States and examined caries progression among minority,[16] rural,[23] and low income[12,23,24] children, while our study included a more diverse sample where the majority of children had private health insurance. Follow-up periods ranged between 12 months[12,16] to three years.[24] All but one study[24] used a prospective design. Two studies[16,23] incorporated MS testing at baseline into the study protocol with conflicting findings. Fontana et al.[16] studied 396 healthy 18- to 36-month-olds. At 12 months, 23 percent of children had caries increment. However, MS levels, baseline caries experience, and oral hygiene did not predict caries progression in this sample. On the other hand, Warren et al.[23] followed 212 infants and toddlers six to 24 months old; MS was present in 15 percent and 44.5 percent of the sample at study entry and 18 months, respectively. At 18 months, those with MS were 4.4 times more likely to have caries compared to those who were free of MS. Of the five studies[25-29] conducted in Europe, all but one[28] was conducted in a Nordic country and three[26,28,29] used a prospective design. On average, follow-up duration was longer and ranged between three[28] and eight[27] years. Of these, two studies[26, 27] employed MS testing and both reported that MS was predictive of caries. Collectively, our findings add to the growing body of literature suggesting that MS culture of young children at the initial dental visit may help predict caries risk over time and be similarly utilized by pediatric primary care personnel.

Inherent limitations of this study stem from it being conducted in an active multipractitioner office with an essential commitment to providing comprehensive care according to clinical guidelines established by the American Academy of Pediatric Dentistry and practitioner standards established by the ABPD.[7,8] This office-based clinical study reflects real world interpractitioner variability in the diagnosis of carious lesions, as clinicians were not standardized. However, the threshold of cavity detection across the seven Board-certified pediatric dentists is likely relatively uniform, given that patients are shared and differences in treatment plans are discussed and resolved among the practitioners.

Unknown from the current work is whether the caries management approach employed by the CDA dental practice was ineffective or whether caries progression in children with TNTC MS would have been even greater were it not for the clinical interventions employed. Ethical mandates required that children deemed to be at high risk for caries increment must be treated through counseling and use of topical fluorides.

Because caries is a multifactorial, diet-dependent, fluoride-mediated disease with genetic and behavioral susceptibility components, some children with TNTC salivary MS levels may not, in fact, be at risk for cavity initiation or progression. Additionally, some children with extant cavity experience at baseline but no recoverable MS may have benefitted from home care that effectively arrested the caries process prior to initiating dental care at CDA. Thus, multiple opportunities for misclassification of caries activity based solely on MS levels are possible. Nonetheless, children with TNTC MS levels at baseline experienced both greater odds of having cavities at baseline and of having caries increments over time.

While low-income children, identified as Medicaid and CHIP beneficiaries, had higher rates of caries and were more likely to have high salivary MS levels at baseline, the prediction models suggest that being poor or low-income is not an independent risk factor for caries increments. Our prior work examining risk models similarly demonstrated that removal of low-income status as a predictive variable enhanced sensitivity and specificity in caries identification.[17]

We used a recognized extreme groups approach[30, 31] to retrospectively compare the caries experience of children at both ends of the MS spectrum (zero and TNTC). We intentionally omitted data from children with levels at intermediary to zero and TNTC in order to most effectively assess the value of MS testing in caries prediction. However, while zero MS represented almost half of the children who received care at CDA, children with TNTC MS represented only a small minority of children. Therefore, these results must be interpreted with some caution. However, given the promising predictive findings of the current work, further study is warranted to assess the longitudinal caries progression trajectories of children with intermediary MS levels. It is likely that children with intermediary levels will require greater clinical judgment in anticipating caries trajectories than children at the extremes.

Conclusion

Based on this study's findings, the following conclusions can be made:

1. Salivary culture of mutans streptococci in children six years old and younger is a clinically useful tool for the identification of those at high risk for caries occurrence and progression.
2. Income level, as identified by the surrogate Medicaid/CHIP coverage, was not predictive of cavity increment when other variables were considered.
3. Dental and pediatric primary care medical providers should consider culturing of salivary MS to identify children who would benefit from timely dental care and intensive caries management.

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