COHORT STUDY

Retrospective Analysis of Candida-related Conditions in Infancy and Early Childhood Caries

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Abstract: ***Purpose:*** *The purpose of this study was to assess whether there is an association between oral thrush or other Candida-related conditions in infancy and early childhood caries (ECC) diagnosed by pediatricians.* ***Methods:*** *We conducted a retrospective cohort study using electronic health records from six national children's hospitals that participate in the PEDSnet research network. There were 1,012,668 children with a visit at ages one to 12 months and another visit at ages 13 to 71 months. The independent variables were diagnosis of thrush or Candida-related conditions in the first year of life, while the dependent variable was diagnosis of ECC between 13 to 71 months old.* ***Results:*** *Oral thrush detection was strongly associated with ECC, particularly between 13 and 36 months (rate ratio between 2.7 [95 percent confidence interval (95% CI) equals 2.5 to 2.9; P<.001] and 3.0 [95% CI, equals 2.8 to 3.4; P<.001]). A similar trend was observed with other Candida-related conditions.* ***Conclusions:*** *Oral thrush may be a risk factor for early childhood caries.* *(Pediatr Dent 2018;40(2):131-5) Received July 6, 2017 | Last Revision November 19, 2017 | Accepted November 21, 2017*

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Early childhood caries (**ECC**) is one of the most prevalent childhood diseases, afflicting 23 percent of the U.S. preschoolers, with significant consequences for the oral and general health and well-being of affected children.[1] Left untreated, ECC can lead to severe carious lesions that may require intervention under general anesthesia. Importantly, even after restoration of carious teeth, children remain at high risk for future recurrences, despite preventive fluoride treatment.[1] Therefore, identifying children at risk for ECC along with providing early intensive preventive dental care and maintenance of oral health are essential to fight this painful and costly disease.

The etiology of ECC is multifactorial, involving interactions between oral microorganisms, diet, and the host, leading to the establishment of caries-causing biofilms on susceptible tooth surfaces. Sugar-laden dietary habits trigger colonization of the teeth by cariogenic bacteria, such as *Streptococcus mutans*, and further development of an acidogenic-aciduric microbiota, both of which are primary factors associated with the onset of the disease.[2] Intriguingly, recent evidence suggests that the microbiome associated with ECC may also include fungal species. Several clinical studies have shown that *Candida albicans* is frequently detected in high numbers in the saliva and plaque from toddlers with ECC, and its presence has been associated with the severity of the disease.[3-6] By contrast, *C albicans* is either absent or detected sporadically in ECC-free children. Given the infectious nature of the disease and the available microbiological evidence of *Candida* involvement, the question arises of whether early diagnosis of *Candida*-related conditions, such as oral thrush, in the pediatric setting can be an identifiable risk factor for ECC.

Pediatricians are often the first health professionals to encounter ECC, as young children are far more likely to visit primary care physicians than dentists.[7] Furthermore, recent availability of large-scale electronic health record (**EHR**) databases in hospital settings, such as PEDSnet,[8] provides an unparalleled opportunity for observational studies. Thus, the purpose of this retrospective study, using a large electronic health record (PEDSnet) dataset, was to investigate whether an infection with *Candida* early in a child's life (i.e., the first year) puts him/her at high risk for development of early childhood caries. If such an association is found, *Candida* infections can be considered a risk factor for ECC, which may affect the way that these infections are managed along with the intensity of anticaries preventive measures applied.

Methods

Data source. The data for this study were obtained from PEDSnet, a network of children's hospitals developed with the goal of creating an interconnected research infrastructure to conduct a wide variety of scientific observational and interventional studies in pediatrics.[9] PEDSnet has integrated EHR data for greater than six million children from large children's hospital systems, including Children's Hospital of Philadelphia, Children's Hospital Colorado, Nemours Children's Health System, Nationwide Children's Hospital, Seattle Children's Hospital, and Boston Children's Hospital. The diagnoses data in PEDSnet represent physician-recorded diagnoses in the EHRs, including a primary or secondary diagnosis, during a clinical encounter or annotated in the patients' problem list entry. In

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PEDSnet, the diagnosis data is standardized using the Systematized Nomenclature of Medicine—Clinical Terminology (**SNOMED-CT**), a terminology with significantly greater granularity than the International Classification of Diseases. By aggregating and standardizing large amounts of high quality clinical data and updating periodically, PEDSnet is a powerful data resource for a variety of research uses.[10-12] We used the May 2016 release of the PEDSnet for this study.

Study population. This study was reviewed and approved by the Institutional Review Board of Children's Hospital of Philadelphia, Philadelphia, Pa., USA. Children's records were eligible if they had their first hospital visit on or after January 1, 2009, at least one hospital visit between one and 12 months old, and at least one additional hospital visit between 13 and 71 months old.

Data retrieval and study design. Data from visits between one and 12 months old were used to characterize potential predictors of ECC (i.e., *Candida* conditions), while visits between 13 and 71 months were used to assess ECC outcomes. The independent variables were classified as primary (diagnosis of thrush in first year of life) and secondary (diagnosis of any *Candida*-related conditions such as candidiasis). The dependent variable was diagnosis of ECC between 13 and 71 months old.

Clinical diagnoses. In PEDSnet, a diagnosis is recorded using a SNOMED-CT code. The study team developed a code-set for each condition of interest, including ECC, thrush, and any candidiasis, as listed in Appendices 1, 2 and 3. A patient is considered to be diagnosed with a certain condition if he/she is associated with at least one relevant SNOMED-CT code in the data source within a given time frame. It should be noted that any candidiasis code-set subsumes the thrush code-set. In addition, while a particular diagnosis may be recorded multiple times for a given patient, the analyses count a patient only once within a time frame.

Data analysis. Data extraction and management were done using PostgreSQL 9.5.3 software (PostgreSQL Global Development Group, https://www.postgresql.org) and Oracle 12c (Redwood Shores, Calif). Statistical analyses were done using R 3.2.4 software (The R Foundation for Statistical Computing, Vienna, Austria). Results are reported as rate ratios with 95 percent confidence intervals (**95% CIs**) and *P*-values using Pearson's chi-squared test with Monte-Carlo simulation done using 10,000 iterations.

Results

A total of 1,012,668 children were identified who were seen as infants (between the ages of one and 12 months) and had at least one more hospital visit between ages 13 to 71 months at six hospital sites. From those children, 33,752 (3.33 percent) were diagnosed by hospital pediatricians as having ECC. The rate ratios of ECC diagnosis (i.e., the identification of the disease within each year of the first six years of life) in children with and without a diagnosis of thrush in the first year of life are seen in Table 1. The data revealed that oral thrush diagnosis in infancy is strongly associated with ECC detection in every year following the first year of life but especially at younger ages (i.e., between 13 to 36 months), when rate ratios were between 2.7 (95 percent CI equals 2.5 to 2.9; *P*<.001) and 3.0 (95% CI equals 2.8 to 3.4; *P*<.001). Furthermore, we observed an intriguing trend regarding the timeline of the rate ratios of ECC and oral thrush diagnosis. While the rate ratios remained statistically significant in every year, the highest rate ratio was observed in the second year, which gradually reduced over time with the lowest in the sixth year (Table 1).

The average rate ratio between the two groups (children with ECC and history of thrush/children with ECC and no history of thrush) at all ages (13 to 71 months) was 2.14, which was statistically significant (95% CI equals 2.1 to 2.2; *P*<.001). A similar trend was observed with any *Candida*-related infections (grouped as candidiasis; Table 2). Children diagnosed with any form of candidiasis in the first year of life had a 2.4 times (95% CI equals 2.2 to 2.5; *P*<.001) to 2.6 (95% CI equals 2.4 to 2.8; *P*<.001) times greater ECC diagnosis within the first three years of life. The outcome was consistent across the different hospital sites included in PEDSnet (data not shown). Although thrush is mainly a disease that affects infants (first year of life), some children were affected later than their first year of life with this infection. When that set of children was added to those affected in their first year of life and observed, the average rate ratio was found to be even higher (rate ratio equals 2.3; 95% CI equals 2.2 to 2.4; *P*<.001) and the difference remained statistically significant.

Table 1. RATE RATIOS OF EARLY CHILDHOOD CARIES DIAGNOSIS IN CHILDREN 13 TO 71 MONTHS OLD WITH A POSITIVE ORAL THRUSH DIAGNOSIS BETWEEN ZERO AND 12 MONTHS OLD

Age (mos.)	Rate (per 1,000)			
	Children with positive thrush diagnosis * (0-12 mos.)	Children with negative thrush diagnosis † (0-12 mos.)	Rate ratio (95% CI)	*P*-value
13-24	10.86	3.55	3.06 (2.78-3.36)	<.001
25-36	20.68	7.62	2.71 (2.53-2.90)	<.001
37-48	21.36	9.47	2.25 (2.11-2.41)	<.001
49-60	16.14	8.79	1.84 (1.70-1.98)	<.001
61-71	11.04	6.21	1.78 (1.62-1.95)	<.001

* Total number of children with a positive thrush diagnosis; N=44,105.

† Total number of children with a negative thrush diagnosis; N=968,563.

Table 2. RATE RATIOS OF EARLY CHILDHOOD CARIES DIAGNOSIS IN CHILDREN 13 TO 71 MONTHS OLD WITH A POSITIVE CANDIDIASIS DIAGNOSIS BETWEEN ZERO AND 12 MONTHS OLD

Age (mos.)	Rate (per 1,000)			
	Children with positive candidiasis diagnosis * (0-12 mos.)	Children with negative candidiasis diagnosis † (0-12 mos.)	Rate ratio (95% CI)	*P*-value
13-24	8.82	3.41	2.58 (2.38-2.79)	<.001
25-36	17.30	7.35	2.35 (2.22-2.49)	<.001
37-48	18.11	9.24	1.96 (1.86-2.07)	<.001
49-60	14.17	8.64	1.64 (1.54-1.74)	<.001
61-71	9.43	6.13	1.54 (1.43-1.65)	<.001

* Total number of children with a positive candidiasis diagnosis; N=85,020.

† Total number of children with a negative candidiasis diagnosis; N=927,648.

Discussion

Our results suggest that early oral thrush may place children at high risk for developing ECC. Among approximately one million children, those diagnosed with thrush in the first year of life were about three times more likely to be diagnosed with ECC by a pediatrician early on, suggesting that thrush could serve as a potential caries risk factor that could be identified by pediatricians. This data is congruent with clinical findings that *C albicans* are often detected in plaque and saliva from ECC-affected children.[3-6,13,14] Furthermore, a recent study showed a strong relationship between the *Candida* infections of caregivers (biological mothers) and their children's fungus levels in plaque, along with the severity of ECC.[14] In particular, children with severe ECC and their mothers appear to be infected with high levels of *C albicans.* Most importantly, the fungal strains are genetically related, indicating that the sources of *C albicans* infections in children are their mothers.[14]

Colonization of the neonates with *Candida* has been shown to occur as early as within 72 hours post-delivery through the mother's vaginal tract.[15-17] Vulvovaginal candidiasis occurs in 75 percent of women during their reproductive years and in 30 to 40 percent of them during pregnancy.[15,16] However, the majority of colonized neonates remain asymptomatic, and only five to seven percent of them develop thrush,[18] which is consistent with the 4.36 percent of children in our cohort who had a history of thrush in their first year of life. Given the potential role of *C albicans* in the development of ECC, neonatal *Candida* infection may have important implications in the oral health of children and needs to be explored in future longitudinal clinical studies.

From the cohort, 33,752 children (3.33 percent) were diagnosed by hospital pediatricians as having ECC, which provides one the few reports of ECC diagnosed by pediatricians. The prevalence of ECC has recently been reported to be 23 percent,[19] although it can vary from 18 to 42 percent depending on socioeconomic status.[7] While large cavities can be easily detected by a medical provider, small or white spot lesions are certainly more difficult to be identified or differentiated from caries-free tooth surfaces. This could at least in part explain the large discrepancy between the diagnosis of ECC by pediatricians in our cohort and ECC prevalence reported in the literature. This finding points to the need for improving caries diagnostic tools for early detection as well as enhancing medical-dental interactions.

Early intervention by pediatricians is important, because they are often the first health professionals to encounter ECC; therefore, they could play a pivotal role in helping to prevent childhood caries. Indeed, according to the Medical Expenditure Panel Survey, 89 percent of children younger than 12 months had office-based physician visits annually versus only two percent who had dental visits.[20] Pediatricians could provide consultation to avert practices associated with an increased risk for ECC and refer patients with advanced clinical signs of ECC to dentists. However, today there are not reliable caries risk assessment tools; therefore, the identification of children at risk for ECC before the onset of cavitation in the pediatric office remains challenging. Here, we made an observation that oral thrush and other *Candida* infections are strongly associated with ECC. This finding, once validated, could lead to early intensive preventive care and strengthen the medical-dental interaction. Pediatricians could refer children affected with oral thrush to dentists in order to implement anti-caries measures, thereby reducing the chance of further ECC development.

The strength of this study, although being an observational report, is the large size of its cohort, which includes more than one million children from multiple pediatric hospital locations and highly significant association between early oral thrush detection and ECC. Conversely, we recognize the limitations of this study, which include under-diagnosis of ECC by pediatricians and the influence of other covariates on ECC prevalence, such as socioeconomic status and dietary practices. Variations in the number of encounters/medical visits per year at specific ages or other factors, such as medical conditions and systemic treatments (i.e., antibiotic or antifungal use as well as immunosuppression), may also have affected the prevalence of ECC and thrush reported at different time points. The influence of these variables should be assessed in future (longitudinal) studies.

Conclusions

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

1. Oral thrush and other *Candida* infections early in life are strongly associated with pediatrician-diagnosed early childhood caries.
2. While the national average of ECC is 23 percent, pediatricians could only diagnose 3.33 percent of children affected by the disease.

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Appendices

Appendix 1. SNOMED Codes Related to the Concept "Early Childhood Caries"

Code	Name	Code	Name
699489009	Dental caries class I	95252008	Secondary dental caries associated with failed or defective dental restoration
95247003	Salivary dysfunction caries secondary to medication	109571003	Primary dental caries, indeterminate origin
109576008	Primary dental caries, root surface origin	95248008	Salivary dysfunction caries secondary to radiation therapy
109574006	Primary dental caries, nonproximal smooth surface origin	703339005	Moderate cavitated lesion limited to outer half of dentin
109572005	Primary dental caries, cervical origin	699494009	Dental caries class V
196302008	Chronic enamel dental caries	699491001	Dental caries class III
163152009	O/E - dental caries	442231009	Caries involving multiple surfaces of tooth
109564008	Dental caries associated with enamel hypomineralization	95246007	Salivary dysfunction caries secondary to aging
109580003	Caries of infancy associated with breast feeding	109566005	Dental caries associated with enamel hypoplasia
109573000	Primary dental caries, proximal smooth surface origin	234976000	Rampant dental caries
1085951000119102	Dental caries on pit and fissure surface limited to enamel	80967001	Dental caries
1085971000119106	Dental caries on pit and fissure surface penetrating into pulp	699490000	Dental caries class II
711173006	Pit and fissure caries	30512007	Cementum caries
702402003	Early childhood caries	1085981000119109	Dental caries on smooth surface limited to enamel
109568006	Dental caries secondary to developmental defects of tooth structure	95249000	Salivary dysfunction dental caries
		699683004	Nonrestorable carious tooth
109578009	Caries of infancy	196298000	Acute dentine dental caries
109577004	Primary dental caries, multisurface origin	1085961000119100	Dental caries on pit and fissure surface penetrating into dentin
109569003	Dental caries secondary to acquired defects of tooth structure	109575007	Primary dental caries, pit and fissure origin
1085991000119107	Dental caries on smooth surface penetrating into dentin	442551007	Dental caries extending into dentin
109581004	Caries of infancy associated with bottle feeding	196299008	Chronic dentine dental caries
702646000	Extensive cavitated lesion with exposed dentine	196305005	Odontoclasia
700046006	Carious exposure of pulp	1086001000119108	Dental caries on smooth surface penetrating into pulp
95254009	Secondary dental caries	80753001	Arrested dental caries
80353004	Enamel caries	699492008	Dental caries class IV
716364007	Caries of cervical margin of tooth	711174000	Interproximal enamel caries
711175004	Caries of smooth surface of tooth	196301001	Acute enamel dental caries
95253003	Secondary dental caries associated with local or systemic factors	699495005	Dental caries class VI
		15733007	Incipient enamel caries

Appendix 2. SNOMED Codes Related to the Concept "Thrush"

Code	Name
79740000	Candidiasis of mouth
110277001	Hyperplastic thrush
235072005	Chronic hyperplastic candidiasis
235069003	Acute oral pseudomembraneous candidiasis
235070002	Acute oral atrophic candidiasis
235071003	Oral erythematous candidiasis
30799000	Neonatal thrush
278521000	Candida angular cheilitis
421710003	Candidiasis of mouth associated with AIDS
359757004	Chronic atrophic candidiasis
402996006	Chronic pseudomembranous oral candidiasis
402997002	Chronic plaque-like oral candidiasis
402998007	Chronic nodular oral candidiasis
95893008	Pseudomembranous thrush
95894002	Atrophic thrush
713497004	Candidiasis of mouth co-occurrent with human immunodeficiency virus infection
3001000119103	Candidiasis of tongue
707318002	Chronic multifocal candidiasis of mouth

Appendix 3. SNOMED Codes Related to the Concept "Candidiasis"

Code	Name	Code	Name	Code	Name
20639004	Candidiasis of the esophagus	240705002	Candidiasis of trachea	432480003	Candidemia associated with intravascular line
79740000	Candidiasis of mouth	240709008	Perineal candidiasis	72605008	Candidal vulvovaginitis
111904009	Candidiasis of urogenital site	240716009	Familial chronic mucocutaneous candidiasis - recessive type	421047005	Candidiasis of lung associated with AIDS
187014000	Candidiasis of skin and nails	240717000	Familial chronic mucocutaneous candidiasis - late onset type	421710003	Candidiasis of mouth associated with AIDS
84679006	Gastrointestinal candidiasis	240719002	Chronic diffuse mucocutaneous candidiasis	421077004	Disseminated candidiasis associated with AIDS
72934000	Candidiasis of vagina	240720008	Central nervous system candidiasis	359736007	Candidal perionyxis
3487004	Candidiasis of lung	240706001	Candida infection of genital region	359757004	Chronic atrophic candidiasis
63553008	Candidal endocarditis	240708000	Penile candidiasis	402131002	Disseminated cutaneous candidiasis
78048006	Candidiasis	240723005	Chronic disseminated candidiasis	402132009	Systemic candidiasis with skin involvement
70572005	Invasive candidiasis	187017007	Candidal paronychia	403001004	Chronic acquired mucocutaneous candidiasis
414821002	Neonatal candidiasis	279325003	Submammary monilia	402996006	Chronic pseudomembranous oral candidiasis
426507006	Enteritis due to Candida	29147005	Mucocutaneous candidiasis	402997002	Chronic plaque-like oral candidiasis
1085006	Candidiasis of vulva	234568006	Chronic mucocutaneous candidiasis	402998007	Chronic nodular oral candidiasis
110277001	Hyperplastic thrush	235072005	Chronic hyperplastic candidiasis	402999004	Nodular candidiasis of diaper area
11244009	Polyglandular autoimmune syndrome, type 1	235073000	Familial chronic mucocutaneous candidiasis	403000003	Neonatal systemic candidiasis
129672005	Localized candidiasis	235069003	Acute oral pseudomembraneous candidiasis	83062006	Infection by Candida albicans
236721000	Candiduria	235070002	Acute oral atrophic candidiasis	95893008	Pseudomembranous thrush
230213004	Candidal brain abscess	235071003	Oral erythematous candidiasis	95894002	Atrophic thrush
232406009	Chronic pharyngeal candidiasis	237070001	Uterine candidiasis	432261003	Candidemia
232404007	Acute pharyngeal candidiasis	237082005	Candidiasis of cervix	231990003	Candida retinitis
23484007	Candidiasis of nails	266154004	Candidiasis of mouth and esophagus	713297001	Candidiasis of esophagus co-occurrent with human immunodeficiency virus infection
197903003	Candidal urethritis	266157006	Perianal candidiasis	713497004	Candidiasis of mouth co-occurrent with human immunodeficiency virus infection
206356004	Neonatal candidiasis of perineum	426762000	Candidiasis of nipple	715593000	Infection of nasal cavity caused by Genus Candida
206358003	Neonatal candidiasis of intestine	266158001	Candidal intertrigo	447841007	Sepsis due to Candida
206359006	Neonatal candidiasis of lung	34786008	Candidal proctitis	10840100011910	Ductal candidiasis of breast
240704003	Pharyngeal candidiasis	30799000	Neonatal thrush	3001000119103	Candidiasis of tongue
240707005	Anogenital candidiasis	278521000	Candida angular cheilitis	707318002	Chronic multifocal candidiasis of mouth
240710003	Granuloma gluteale infantum	416282001	Ocular candidiasis	708126004	Recurrent candidiasis of vagina
240714007	Familial chronic mucocutaneous candidiasis - dominant type	49883006	Candidiasis of skin	700455003	Gingivitis due to Genus Candida
240718005	Chronic localized mucocutaneous candidiasis	276672007	Congenital candidiasis		
240721007	Renal tract candidiasis	52643007	Candidal balanitis		
240711004	Diaper candidiasis	52914002	Anal candidiasis		
240713001	Candidiasis of finger web				
240722000	Acute disseminated candidiasis				