



Published in final edited form as:

Pediatr Dent. 2018 March 15; 40(2): 131–135.

Retrospective analysis of Candida-related conditions in infancy and early childhood caries

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Abstract

Purpose—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.

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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 at ages 13 to 71 months. The independent variables were diagnosis of thrush or *Candida*-related conditions in first year of life, while the dependent variable was diagnosis of ECC between 13–71 months of age.

Results—Oral thrush detection was strongly associated with ECC, particularly at ages between 13–36 months (rate ratio between 2.7 [95 percent Confidence Interval (CI), 2.5–2.9; P<.001] and 3.0 [95 percent CI, 2.8–3.4; P<.001]). A similar trend was observed with other *Candida*-related conditions.

Conclusions—Oral thrush may be a risk factor for ECC.

Early childhood caries (ECC) is one of the most prevalent childhood diseases, afflicting 23 percent of the US preschoolers, with significant consequences for the oral and general health and well-being of affected children¹. Left untreated, ECC can lead to severe carious lesions that may require intervention under general anesthesia and importantly, even after restoration of carious teeth, children remain at high risk for future recurrences despite preventive fluoride treatment¹. Therefore, identifying the children at risk for ECC along with 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 disease². 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, 4, 5, 6}. In 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 dentists⁷. Furthermore, recent availability of large-scale electronic health record (EHR) databases in hospital settings, such as PEDSnet⁸, provides an unparalleled opportunity for observational studies. Thus, we conducted a retrospective study using a large EHR (PEDSnet) dataset 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 ECC. 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 was 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 pediatrics⁹. 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 represents 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 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^{10,11,12}. We used the May 2016 release of the PEDSnet for this study.

Study Population

The study was reviewed and approved by the Children's Hospital of Philadelphia Institutional Review Board. 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 of age, and at least one additional hospital visit between 13 and 71 months of age.

Data Retrieval and Study Design

Data from visits between one and 12 months of age 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 of age.

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 the 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 was done using PostgreSQL 9.5.3 and Oracle 12c. Statistical analyses were done using R version 3.2.4 (The R Project for Statistical Computing). Results are reported as rate ratios with 95 percent Confidence Intervals (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 13–71 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 13–36 months where rate ratios were between 2.7 (95 percent CI, 2.5–2.9; $P < .001$) and 3.0 (95 percent CI, 2.8–3.4; $P < .001$). Furthermore, we observed an intriguing trend of 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 (13–71 months) was 2.14, which was statistically significant (95percent CI, 2.1–2.2; $P < .001$). 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 (95 percent CI, 2.2–2.5; $P < .001$) to 2.6 (95 percent CI, 2.4–2.8; $P < .001$) 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, 2.3; 95 percent CI, 2.2–2.4; $P < .001$) and the difference remained statistically significant.

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 by a pediatrician with ECC 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^{3,4,5,6,13,14}. Furthermore, a recent study showed a strong relatedness between the *Candida* infections of caregivers (biological mothers) with their children's fungus levels in plaque, along with the severity of

ECC¹⁴. In particular, children with severe ECC and their mothers appear to be infected with high levels of *C. albicans*, and most importantly, the fungal strains are genetically related, indicating that the source of *C. albicans* infections in children is their mother¹⁴.

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^{15,16,17}. 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 thrush¹⁸, which is consistent with the 4.36 percent of children in our cohort that 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 of the few reports of ECC diagnosed by pediatricians. The prevalence of ECC has recently been reported to be 23 percent¹⁹, although it can vary from 18 to 42 percent depending on socioeconomic status⁷. 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, which 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 the medical-dental interactions.

Early intervention by pediatricians is important, because they are often the first health professionals to encounter ECC, and 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 under one-year of age had office-based physician visits annually, compared with only two percent who had dental visits²⁰. Pediatricians could provide consultation to avert practices associated with an increased risk for ECC as well as refer patients with advanced clinical signs of ECC to dentists. However, today there are not reliable caries risk assessment tools, and 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 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 includes underdiagnosis 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, ie., antibiotic or antifungal use as well as immunosuppression, could 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

The results of this investigation support the following conclusions.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported in part by the National Institute for Dental and Craniofacial Research (NIDCR) grant R01DE025220 and R01DE018923 to HK, and PCORI Contract Number CDRN-1306-01556 to CF.

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Table 1

Rate ratios of ECC diagnosis in children 13 to 71 months of age with a positive oral thrush diagnosis between 0 and 12 months of age

Age of the children	Rate (per 1000)		Rate Ratio (95% CI)	P Value
	Children with positive thrush diagnosis* (0 – 12 months)	Children with negative thrush diagnosis** (0 – 12 months)		
–13 – 24 months	10.86	3.55	3.06 (2.78-3.36)	< .001
–25 – 36 months	20.68	7.62	2.71 (2.53-2.90)	< .001
–37 – 48 months	21.36	9.47	2.25 (2.11-2.41)	< .001
–49 – 60 months	16.14	8.79	1.84 (1.70-1.98)	< .001
61 – 71 months	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 ECC diagnosis in children 13 to 71 months of age with a positive candidiasis diagnosis between 0 and 12 months of age

Age of the children	Rate (per 1000)		Rate Ratio (95% CI)	P Value
	Children with positive candidiasis diagnosis* (0 – 12 months)	Children with negative candidiasis diagnosis** (0 – 12 months)		
–13 – 24 months	8.82	3.41	2.58 (2.38-2.79)	< .001
–25 – 36 months	17.30	7.35	2.35 (2.22-2.49)	< .001
–37 – 48 months	18.11	9.24	1.96 (1.86-2.07)	< .001
–49 – 60 months	14.17	8.64	1.64 (1.54-1.74)	< .001
61 – 71 months	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