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Early Childhood Caries Experience Associated with Upper Respiratory Infection in US Children: Findings from a Retrospective Cohort Study

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Abstract

Introduction: Both Early Childhood Caries (ECC) and Upper Respiratory Infection (URI) are infectious diseases. The oral cavity is considered a potential reservoir of respiratory pathogens due to the anatomical proximity between the oral cavity and respiratory system, which implies a potential association between ECC and URI. Hence, this study aimed to evaluate the association between ECC experience and URI incidence in preschool children.

Methods: This retrospective cohort study collected data *via* electronic health records. The exposure was ECC before 3 years of age. The dependent variable was the incidence of URI between 4-6 years of age. To analyze the factors associated with the time-to-event of URI, we used log-rank tests and Cox regression models to compare the survival of URI between the ECC and Caries-Free (CF) groups, adjusting factors including demographic-socioeconomic characteristics and medical conditions. To analyze factors associated with the number of URI episodes, we used negative binomial regression models adjusting for factors mentioned above.

Results: A total of 497 US preschool children were included, with 117 ECC and 380 CF children. More children with ECC (58.1%) developed URI than the CF group (47.6%) during the follow-up period (4-6 years of age) (p=0.04). The ECC children were at 1.6 times higher risk to develop URI than the CF children even after accounting for other URI risk factors (Hazard Ratio 1.57 (1.13, 2.10), p=0.007).

Conclusions: Our study suggests a potential association between ECC and URI, with an inference that early life ECC experience could be used as a predictor for developing URI in preschool age. The causal relationship between ECC and URI incidence in young children needs to be investigated through future studies.

Keywords: Early childhood caries; Upper respiratory infection; Pediatric health; Children; Dental Caries

Introduction

Respiratory infection is the first leading cause of death in children younger than 5 years, accounting for over 20% of yearly deaths worldwide [1]. Upper respiratory infection (URI) is an illness caused by an acute infection, which involves the upper respiratory tract, including the nose, sinuses, pharynx, and larynx [2,3]. Intriguingly, recent research implies a potential association between Early Childhood Caries (ECC) and URI.

The American Academy of Pediatric Dentistry defines ECC as the condition of the presence of one or more decayed, missing, filled primary teeth in children between birth and 71 months of age [4,5]. In children younger than 3 years of age, any sign of smooth-surface caries is an indication of Severe Early Childhood Caries (S-ECC) [4]. ECC afflicts approximately 37% of preschool children in the US [6,7] and upto 73% of socioeconomically disadvantaged preschool children in both developing and industrialized countries [8,9]. Many children with S-ECC remain untreated until 3 years of age [10,11], posing an immediate and/or long-term impact on children's oral and general health [10,12].

Both ECC and URI have a microbial involvement. ECC is a chronic infectious disease, initiated by dental plaque/biofilm formation by multiple cariogenic bacteria and yeast in the oral cavity [13,14]. The oral cavity is also considered as a possible reservoir of respiratory pathogens due to the anatomical connection between the oral cavity and the respiratory tract. For example, *Haemophilus influenzae* is found in dental plaques, which is a common pathogen for URI [1]. A study that examine the Medicaid data from Michigan indicates that the occurrence of respiratory infection during the first year of life was associated with a significantly increase risk for developing ECC during the subsequent years [15]. On the other hand, a prospective cohort study conducted among preschool children in Hong Kong showed that the number of URI episodes was inversely associated with children's caries experience [1].

Despite a potential association between ECC and URI, studies

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that examined the association between ECC and pediatric URI are scarce and the findings are inconclusive [1,15]. Hence, our study aimed to evaluate the association between ECC experience and URI incidences among US preschool children using a retrospective cohort design.

Methods

Study design

This retrospective cohort study involved a record (medical and dental) review that was conducted from April 8, 2020 to November 30, 2020. The electronic dental record system (Axium) and medical record system (eRecord EPIC) of 2,325 preschool children, seen at the Eastman Institute for Oral Health (EIOH) and the University of Rochester Medical Center (URMC) were used to screen eligible participants. This study was approved by the University of Rochester Research Subject Review Board (STUDY00004491). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Participants

Both male and female children were included. Participants were divided into two groups based on the exposure (ECC experience before 3 years of age): exposure group (ECC) and non-exposure group (Caries-Free (CF)). The inclusion criteria were: 1) Patients of both Eastman Institute for Oral Health and University of Rochester Medical Center; 2) Between 12-36 months old at the starting point of the study. The Exclusion criteria were: 1) Lack of electronic record in either dental or medical record system; 2) Prior to the study starting point, participants with oral deformities (cleft lip and palate) or any severe systemic diseases including neoplasm, hematological diseases, immune system diseases, lung diseases (e.g., childhood interstitial lung disease, bronchopulmonary dysplasia); 3) Prior to the study starting point, participants who had history of URI.

Data collection

The dental and medical electronic records were searched in the following steps:

- A report generated by the dental record team was provided to the investigators. This report included a list of patients (2,325 preschool children) who were 12-36 months old and had been seen at the EIOH from 07.01.2007 to 07.01.2013.
- The investigators crosschecked whether the eligible participants identified in step 1 had available medical records until 6 years of age.
- The eligibility of potential participants was confirmed using inclusion and exclusion criteria described above.

Outcomes and covariates

The primary outcome (dependent variable) was the incidence of URI between 4-6 years of age. The covariates (independent variables) were: 1) demographic-socioeconomic data including age, sex, race, ethnicity, zip code, and insurance type. The insurance data was obtained using the insurance status at the time of record review. 2) Medical conditions that predispose children at higher risk for infectious diseases, including pediatric sleep apnea, asthma, history of antifungal medication, antibiotics usage, sulfa usage, inhaler use, second-hand smoking exposure and recipient of total oral rehabilitation. The diagnosis of systemic diseases was made by the participants' physician that documented in the medical records. The medical conditions charted were those that occurred before the URI for children who developed URI; or those that occurred before the end of the observational study period for children who did not develop URI. 3) ECC before 3 years of age. The diagnosis of ECC was based on the documentation in dental records, which included any charted decayed or filled teeth/surface (dft/s). The age of the charted dft/s was obtained from the charting of the dental records.

Statistical analysis

Differences between the demographic-socioeconomic-medical-dental characteristics between the exposure and non-exposure groups were compared using Chi-square or Fisher's exact tests for categorical data or t-test for continuous data. Comparisons between the ECC and CF groups, regarding the incidence of URI, ear infection, strep throat, pneumonia, and the severity of URI were conducted using a Chi-square/Fisher's exact test. Additionally, a t-test was used to compare the dft/dfs between the ECC and CF groups at the study endpoint, and to compare the dft/dfs between baseline and endpoint of the ECC group. To analyze the factors associated with time-to-event of URI, we first used log-rank tests to preselect factors that indicate a significant difference in time-to-event between the exposure and non-exposure groups. Furthermore, Cox regression analysis was used to compare the survival of the URI between the ECC and CF groups, adjusting factors including significant factors pre-selected from the log-rank tests, and demographic-socioeconomic characteristics and other commonly recognized confounders for the URI. To compare the number of URI episodes between the ECC and CF groups, we used a negative binomial regression model adjusting the same factors selected for the Cox regression analysis. Statistical analysis was conducted using computerized statistical program SAS statistics software. The significance level was set to 0.05 in the analyses.

Results

A total of 497 children were included in the study, with 117 in the exposure group (ECC) and 380 in the non-exposure group (CF). Among the ECC children, 23.1% had ECC onset before 2 years of age. The Demographic-medical characteristics of the study participants are shown in Table 1. No statistical differences were detected between the ECC and CF group, regarding the demographic-socioeconomic parameters and medical conditions ($p>0.05$). More children with ECC (58.1%) developed URI than the CF group (47.6%) ($p=0.04$).

The oral health conditions of the study children are shown in Table 2. Children in the ECC group had a striking number of decayed and filled tooth surfaces at a young age (1-3 years old), with an average of 11.0 dfs per child. Among the ECC children, more filled teeth/surfaces (ft/s) and less decayed teeth/surfaces (dt/s) were seen at the study endpoint (6 years of age). At the endpoint, ECC children had more filled teeth/surfaces (ft/s) ($p<0.001$), but not more decayed teeth/surfaces (dt/s), than the CF children ($p=0.12$ for dt and $p=0.09$ for ds).

The parameters reflecting URI severity (Table 3) were not significantly different between the ECC and CF groups ($p>0.05$), including the recurrence of URI (27.9% in ECC and 39.8% in CF

Table 1: Demographic-Medical characteristics of study participants.

Variables	Exposure (ECC) (n=117)	Non-Exposure (CF) (n=380)	P-value
Demographic-Socioeconomic Characteristics			
Sex (Female)	64 (54.7%)	197 (51.8%)	0.6
Race (African American)	77 (65.8%)	274 (72.1%)	0.42
Race (White)	29 (24.8%)	75 (19.7%)	
Race (Other)	11 (9.4%)	31 (8.2%)	
Ethnicity (Non-Hispanic)	104 (88.9%)	326 (85.8%)	0.4
Zip code (Above median income)	66 (56.54%)	227 (59.7%)	0.52
Insurance type (State-support)	97 (82.9%)	329 (86.6%)	0.24
Insurance type (Private)	12 (10.3%)	22 (5.8%)	
Insurance type (Self pay)	8 (6.8%)	29 (7.6%)	
Primary Outcome			
URI incidence (Y)	68 (58.1%)	181 (47.6%)	0.04
Secondary outcomes			
Pediatric pneumonia incidence (Y)	10 (8.5%)	25 (6.6%)	0.45
Ear infection incidence (Y)	31 (26.5%)	111 (29.2%)	0.57
Strep throat incidence (Y)	31 (26.5%)	99 (26.1%)	0.92
Covariates			
Total oral rehabilitation (Y)	65 (55.6%)	43 (11.3%)	<.001
Second hand smoking (Y)	25 (21.4%)	84 (22.1%)	0.89
Pediatric sleep apnea (Y)	13 (11.1%)	23 (6.1%)	0.06
Asthma (Y)	30 (25.6%)	96 (25.3%)	0.94
History of antifungal meds (Y)	70 (59.8%)	213 (56.1%)	0.47
History of antibiotics (Y)	89 (76.1%)	275 (72.4%)	0.43
History of inhaler (Y)	47 (40.2%)	143 (37.7%)	0.64
History of sulfa (Y)	16 (13.8%)	51 (13.5%)	0.93

ECC: Early Childhood Caries; CF: Caries Free.

Table 2: Oral health conditions of study participants.

	ECC at baseline (1-3 yrs)	ECC at end-point (4-6 yrs)	CF at end-point (4-6 yrs)	P value ECC (baseline *vs.* end-point)	P value (End-point ECC *vs.* CF)
dt	1.9 ± 3.5	0.2 ± 1.2	0.1 ± 0.6	<0.001	0.12
ft	2.3 ± 3.1	5.0 ± 4.1	2.0 ± 3.0	<0.001	<0.001
dft	4.2 ± 3.7	5.3 ± 4.1	2.1 ± 3.0	0.04	<0.001
ds	3.3 ± 8.2	0.3 ± 1.8	0.1 ± 0.8	<0.001	0.09
fs	7.3 ± 13.0	17.3 ± 17.8	5.6 ± 11.3	<0.001	<0.001
dfs	11.0 ± 13.6	17.6 ± 17.6	5.8 ± 11.3	<0.001	<0.001

ECC: Early Childhood Caries; CF: Caries Free; dt: decayed teeth; ds: decayed surface; ft: filled teeth: fs: filled surface; dft: decayed and filled teeth; dfs: decayed and filled surface.

groups), medication prescribed to treat URI related symptoms, and the medical department when children with URI were seen. Pain or fever-reducing medications were commonly prescribed among 43.3-51.6% of children who had URI. Although most children seek care at their primary care physician's office, approximately 20% of the children were seen at the Emergency Department (ED) for their 1st URI episode. The percentage of children who seek care at the ED was less among the 3rd-6th URI episodes than the 1st-2nd URI episodes.

Survival estimation of the factors associated with the URI time-to-event

From the log-rank tests, we identified individual variables that were associated with the URI time-to-event. We further plotted the survival curve to visualize their impact (Figure 1). The model estimated that the 5-year survival among the ECC group was approximately 50%, which was significantly lower than the survival of the CF group (60%) (p=0.0007, Figure 1A). The URI survival was marginally associated with receiving total oral rehabilitation (Figure 1B, p=0.05). Additionally, the 5-year survival was significantly lower among children with a history of inhaler use (Figure 1C, p<0.001) and antibiotic medication usage (Figure 1D, p<0.001), comparing to their counterparts.

Second, a Cox regression analysis was used to provide an effect

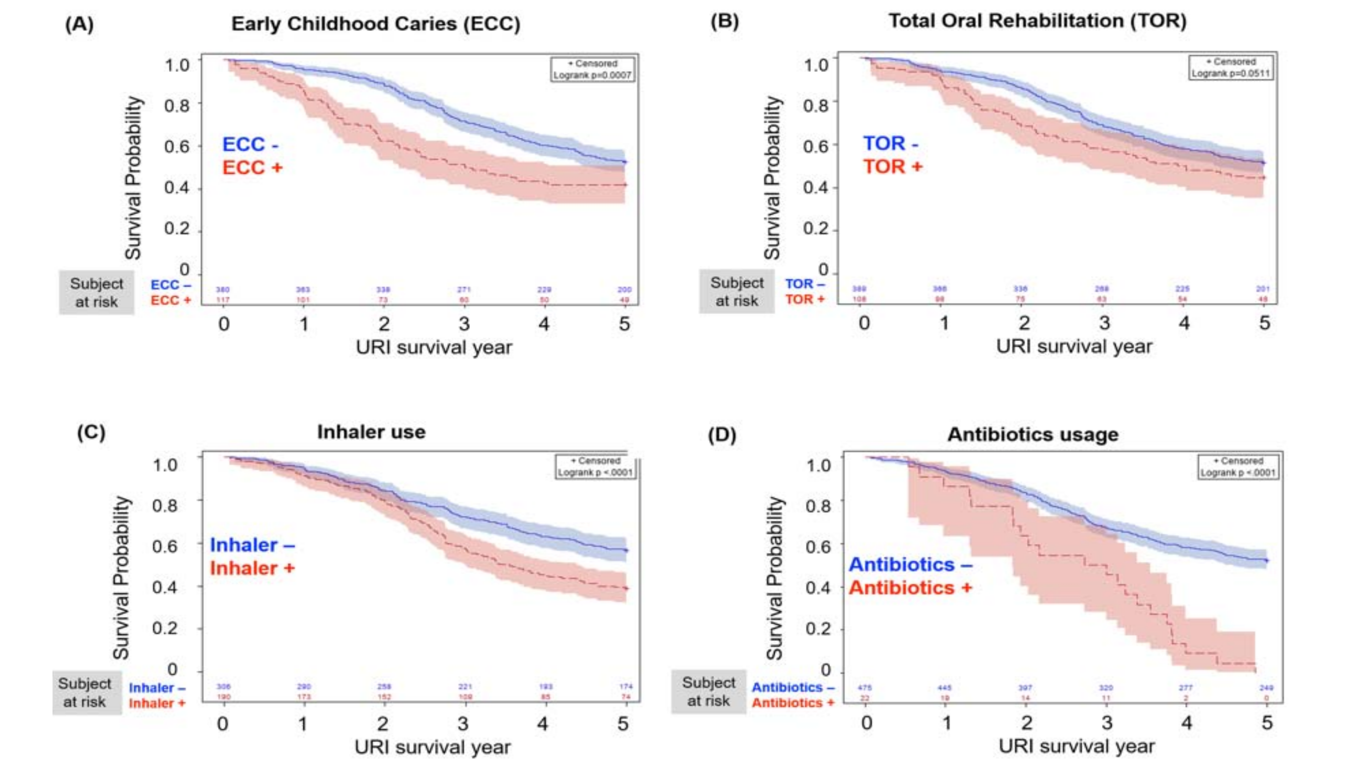

Figure 1: URI survival probability estimation. A) 5-year URI survival estimation between the children with Early Childhood Caries (ECC) and Caries-Free (CF) (p=0.0007); B) 5-year URI survival and total oral rehabilitation (p=0.05); C) 5-year URI survival and inhaler use (p<0.0001); D) 5-year URI survival and history of antibiotic usage (p<0.0001).

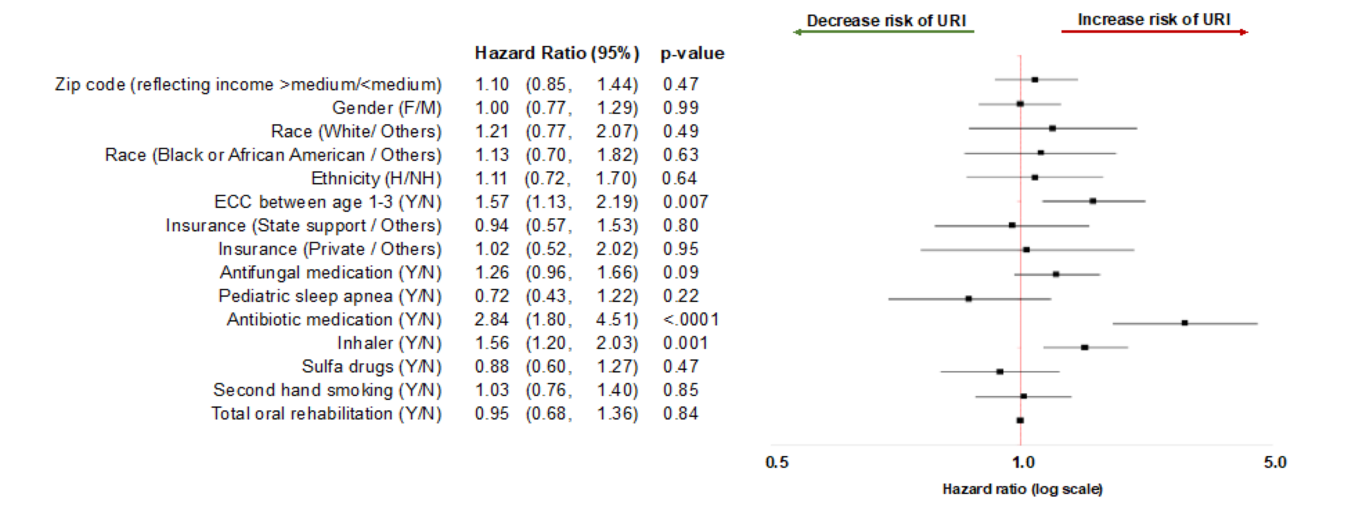

Figure 2: Factors associated with URI time-to-event. A Cox regression analysis was used to examine the factors that were associated with the URI event time in the study population. Our study results indicate that several factors were associated with a higher risk of developing URI, which could be used as risk indicators for URI survival in the pediatric population.

estimate by quantifying the difference in survival between study groups and adjusted for confounding effects of variables (Figure 2). The risk of developing URI was positively associated (p<0.05) with ECC before 3 years of age (Hazard Ratio 1.57 (1.13, 2.19), p=0.007), history of inhaler use (HR 1.56 (1.20, 2.03), p=0.001), and history of antibiotic usage (HR 2.84 (1.80, 4.51), p<0.0001).

Factors associated with the number of URI episodes

We ran a negative binomial regression to analyze factors that were associated with the number of URI episodes, results shown in Supplementary Table 1. Two factors were identified to be associated with an increased number of URI episodes among study participants: history of antibiotic usage (Incidence rate ratio 0.22 (0.22, 1.06),

Table 3: Upper Respiratory Infection Severity.

Variables	ECC (n=117)	CF (n=380)	P-value
Recurrence of URI (yes)	19 (27.9%)	72 (39.8%)	0.07
Medication			
Pain or fever reducing medication (e.g., acetaminophen or ibuprofen)	29 (43.3%)	94 (51.6%)	0.14
Albuterol	2 (3%)	9 (4.9%)	
No meds	32 (47.8%)	71 (39%)	
Medical department (1st URI, n=249)			
Primary care physician	52 (77.6%)	146 (80.2%)	0.65
Emergency department	15 (22.4%)	36 (19.8%)	
Medical department (2nd URI, n=91)			
Primary care physician	14 (73.7%)	61 (84.7%)	0.26
Emergency department	5 (26.3%)	11 (15.3%)	
Medical department (3rd-6th URI, n=42)			
Primary care physician	4 (100%)	35 (88%)	0.52
Emergency department	0 (0.0%)	3 (12%)	

ECC: Early Childhood Caries; CF: Caries Free.

p=0.003) and history of inhaler use (Incidence rate ratio 0.11 (0.22, 0.66), p=0.0001). ECC experience before 3 years of age was not found to be associated with the number of URI episodes (Incidence rate ratio 0.15 (-0.31, 0.17), p=0.43).

Discussion

Children's oral health is a critical component of the overall health and well-being [13]. This retrospective cohort study examined factors associated with developing URI among 497 US preschool school children and revealed a novel finding that the risk of developing URI was higher among children with ECC than those who were caries free in early life. Our findings indicate that early life ECC experience might be used as a predictor for pediatric URI event during the preschool age, and controlling ECC might play a role in reducing the risk of developing pediatric URI.

The following limitations should be considered when interpreting the study results.

1) The data collected on medical conditions were measured as binary variables, hence the severity of those conditions was not taken into account to measure the confounding effects. 2) The study results cannot be generalized to other populations residing outside of the Rochester, NY area. 3) Since we only had access to the medical and dental information from the electronic record in one academic institute, study participants might have seen medical or dental providers outside of the electronic system we accessed. Therefore, the study results might underestimate or overestimate the associations observed.

Several pathways are speculated to link the ECC and URI among young children. One of the pathways is the anatomical connection between the oral cavity and respiratory tract, since the oral cavity might act as a reservoir for respiratory opportunistic pathogens [1]. However, due to the nature of the retrospective study design, we were not able to assess oral and respiratory microorganisms of the study participants that were not included in the medical/dental records. Hence, a mechanistic association between ECC and URI, such as microbial involvement, cannot be explicated. A second suspect linkage between the ECC and increased risk for URI is an alternated immune system of children with dental caries in early life. A recent study by Baker et al. [16], evaluated the host immunological markers and the potential linkage between oral bacteria and these markers during caries development. Ten immunological markers were detected at a higher level in children with active caries than those in CF children [16], suggesting that children with ECC might have altered systemic immunity that could pose a higher risk for developing systemic diseases, e.g., URI.

Worth noting that our finding of the higher risk for developing URI among the ECC children than the CF children, differs from the finding from Zhou et al. [1], where caries severity (dmft score) was inversely associated with the number of URI episodes over 12 months. The reasoning could be the followings: 1) our study had a more extended observational period than the study from Zhou et al. (3 years *vs.* 1 year); 2) moreover, in the study of Zhou et al [1], the URI was self-reported by the parents as having fever, cough, chill, headache, sore throat, runny nose, and muscle pain; whereas the diagnosis of URI in our study was made by participants' physician. The difference in observation time and URI diagnostic criteria could contribute to the opposite findings from us and Zhou et al. [1].

Furthermore, researchers have examined the association between ECC and URI from a different angle. Alaki et al. [15] questioned whether children with URI could increase the risk of ECC. Their study indicated a positive association between having respiratory infection during the first year of life and developing ECC in the following 3 years (HR=1.34, p<0.001). Additionally, having acute middle ear infection during the first year of life was associated with an increased risk of developing ECC in the follow-up period (HR=1.11, p=0.05).

Moreover, a possible association between asthma and ECC was evaluated by Lindemeyer et al. [17]. The authors found that asthmatic children have a lower dmft score than the non-asthmatic children. However, the relationship between asthma and ECC was not detected in our study [17].

Conclusions

Our study results indicated a positive association between ECC and URI, with an inference that ECC experience before age 3 could be used as a predictor for developing URI during the preschool age. The causal relationship between children's caries experience and URI incidence needs to be investigated through future studies.

Authors' Contributions

Dr. Albelali and Dr. Xiao contributed to study design, data collection, data analysis, data interpretation, and manuscript writing. Dr. Wu and Dr. Malmstrom contributed to data analysis, data interpretation, and critical revision of the manuscript.

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Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available due to individual privacy (HIPPA requirements) but are available from the corresponding author on reasonable request, albeit with private identifiers removed.

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