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Original Article

An Adequate Increase in Incremental Feeding Rate May be Useful in Reducing the Incidence of Parenteral Nutrition-associated Cholestasis in Preterm Infants with Birthweight Less than 1500g

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ABSTRACT

Background: Parenteral nutrition-associated cholestasis (PNAC) is one of the most challenging complications of prolonged parenteral nutrition (PN). Limited data are available regarding the association between enteral nutrition (EN) and PNAC. We aimed to explore the correlation of EN strategies with PNAC in preterm infants with birth weight less than 1500 g.

Methods: A nested case-control study (1:1) was performed including infants with gestational age (GA) < 37 weeks, birth weight (BW) < 1500 g, and duration of PN > 7 days. GA, BW, and duration of PN were used as matching criteria. EN strategies before the onset of PNAC were described. Conditional logistic regression was used to identify the independent association of EN strategies with PNAC.

Results: A total of 66 subjects were studied. Univariate analysis revealed that incremental feeding rate, average feeding amounts, average caloric intake via the enteral route, episodes of EN interruption, and days to start EN were similar before the onset of PNAC between groups. Feeding amounts and caloric intake via the enteral route were also similar at the onset of PNAC between groups. On logistic regression, incremental feeding rate was negatively associated with PNAC (OR: 0.479, 95% CI: 0.272-0.844, p=0.011).

Conclusion: Incremental feeding rate may be associated with the development of PNAC in preterm infants. Our findings suggest that an adequate increase in incremental feeding rate may be useful in reducing the incidence of PNAC in preterm infants with birth weight less than 1500 g.

Keywords: Enteral feeding advancement rates, Enteral nutrition, Extremely low birth weight infants, Parenteral nutrition-associated cholestasis, Very low birth weight infants

Introduction

Parenteral nutrition (PN) is commonly used as a critical nutritional supplement in preterm infants until their immature gut can tolerate enteral nutrition (EN) autonomously (1). While prolonged PN using a soy-based lipid emulsion is thought to play a role in the development of cholestasis in preterm infants (2), especially those with birth weight less than 1500 g, this condition is known as parenteral nutrition-associated cholestasis (PNAC). The incidence of PNAC varies considerably among studies and has not obviously declined in recent decades (3). The exact etiology

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and mechanism remain unclear. Most investigators consider the process to be multifactorial (4). Except for the prolonged administration of PN, other risk factors attributed to the development of PNAC, such as immaturity of the hepatobiliary system, lack of enteral feeding, components of PN, gastrointestinal surgeries, sepsis, and hepatotoxic drugs, have been identified (5-7). The degree to which each of these factors contributes to an infant's cholestasis varies according to many interrelated clinical factors (2). PNAC generally resolves after discontinuation of PN (8), but it has a long-lasting effect on prospective weight gain (1), and in some infants it progresses to persistent liver dysfunction and residual fibrosis leading to liver failure (2).

Several prevention or treatment protocols have been proposed to manage PNAC, for example, ursodeoxycholic acid, cholecystokinin, erythromycin, early enteral feeding, cycling PN, lipid dose reduction, alternative parenteral lipids, and enteral fish oil (2, 9). Currently, early enteral feeding with advancement as tolerated is thought to be the best way to prevent or treat PNAC (2); however, limited data regarding the association between EN and PNAC in preterm infants are available. Repa et al. found that "aggressive" nutrition decreased the incidence of PNAC in extremely low birth weight (ELBW) infants (10), while the "aggressive" nutrition referred to both PN and EN.

We aimed to analyze EN strategies, explore the correlation of EN strategies with PNAC, and ultimately elucidate the optimal EN strategies in the prevention of PNAC among very low birth weight (VLBW) and ELBW infants.

Methods

Study Design and Patients This is a single-center nested case-control study (1:1) conducted in accordance with the Declaration of Helsinki and approved by the Research Ethical Committee of Henan Provincial People's Hospital, People's Hospital of Zhengzhou University [approval no. (2020) No.147] on 19 October 2020. All patient information was de-identified and patient consent was not required. Preterm infants who were admitted to the neonatal intensive care unit (NICU) immediately after birth from July 20, 2018, to October 29, 2020, with gestational age (GA) < 37 weeks, birth weight (BW) < 1500 g, and duration of PN > 7 days were eligible for enrollment. Exclusion criteria were inborn metabolic errors, hepadnaviridae infection, and any primary cholestatic liver diseases.

Chinese Society of Parenteral and Enteral Nutrition (CSPEN) guidelines for nutrition in neonates were used in our center (11). Clinical implementation of PN and EN has been described previously (12). Briefly, individualized PN was prescribed daily. The PN solution containing amino acid (Pediatric Compound Amino Acid Injection 19AA-I, PAA 6%, Qidu, Shangdong, China), lipid (20% Medium and Long Chain Fat Emulsion Injection C6~24, Fresenius Kabi, Wuxi, Jiangsu, China), glucose, minerals, trace elements (Addamel; Fresenius Kabi, Wuxi, Jiangsu, China), water-soluble vitamins (Soluvit; Fresenius Kabi, Wuxi, Jiangsu, China) and fat-soluble vitamins (Vitalipid; Fresenius Kabi, Wuxi, Jiangsu, China) was started within the first 24 hours of life and infused continuously for 24 hours. Minimal enteral nutrition (MEN) was initiated as soon as possible after birth if applicable. A preterm formula (PreNan, Nestle, Germany) or mother's own milk (MOM) was administered through a nasogastric tube intermittently. Breastmilk energy estimates range from 65 to 70 kcal/dL (13). We chose 67 kcal/dL to calculate the energy estimates.

Evaluation and Management of PNAC Total bilirubin (TBI), direct bilirubin (DBI), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bile acid (TBA), alkaline phosphatase (AKP), and γ-glutamyl transpeptidase (GGT) were, as a rule, measured weekly. For infants in stable condition or with good growth, liver function indices were monitored every 2 weeks. TORCH (toxoplasmosis, cytomegalovirus, rubella, herpes) screening was routinely performed after admission for all infants. For infants developing direct hyperbilirubinemia (direct serum bilirubin level ≥ 1 mg/dL), necessary laboratory investigations were performed to identify possible causative factors. Choleretic medications were used once an infant developed direct hyperbilirubinemia of 1 mg/dL or higher. An infant without identifiable known causes of direct hyperbilirubinemia was diagnosed with PNAC. In this study, a total of 285 infants met the eligibility criteria. If cholestasis were defined as direct bilirubin exceeding 2 mg/dL, only 8 infants would qualify for a PNAC diagnosis, resulting in an insufficient sample size. Therefore, cholestasis was defined as direct bilirubin ≥ 1.0 mg/dL with total bilirubin < 5.0 mg/dL or direct bilirubin > 20% of total bilirubin with total bilirubin > 5.0 mg/dL (14). Sepsis evaluation was performed if clinical sepsis was

suspected. Confirmed sepsis was defined as a positive blood culture.

Infants who developed PNAC comprised the case group, while infants with direct bilirubin less than 1 mg/dL comprised the control group. It is reported that young gestational age, low birth weight, and long duration of PN are significant risk factors for PNAC in premature infants (15). Therefore, GA, duration of PN, and BW were chosen as matching criteria. SPSS 24.0 (SPSS, Inc., IBM, Chicago, IL, USA) was used to provide an accurate and optimal method of matching cases to controls in a 1:1 ratio. It was a random process. Each infant in the case group was matched with a control subject on GA (±7 days), duration of PN (±7 days), and BW (±100 g).

Data Collection Data on demographics and potential confounding variables were collected prospectively. Information on the daily amount (ml/kg/d) and type (PreNan or MOM) of EN administered before the development of PNAC was collected. Intravenous lipid formulation, including medium-chain triglyceride/long-chain triglyceride (MCT/LCT) and SMOF lipid (SO, MCT, OO, FO-ILE), was also recorded. Liver function indices were collected at the onset of PNAC in the cases. Indices of the matched controls were collected at the equivalent postnatal age or the closest time to the age at onset of PNAC in the cases. The indices were not the mean or highest value. All these indices were available in the controls.

Statistical Analysis Data were analyzed using SPSS 24.0 (SPSS, Inc., IBM, Chicago, IL, USA). Continuous variables were presented as median (first, third quartile) and compared using the Mann-Whitney non-parametric test or Student's t-test between the two groups. Categorical data were compared using the chi-square test or Fisher's exact test. A p-value < 0.05 was considered statistically significant. We tried to explore the correlation of EN strategies with PNAC in preterm infants with birth weight less than 1500 g. Multivariable analysis was considered. The conditional logistic regression model was chosen on account of the nested case-control study design. Based on univariate analysis, potential factors at a p-value < 0.3, including incremental feeding rate, episodes of EN interruption, enteral intake, and enteral energy, were selected in the model.

Ethical approval

This study approved by the Research Ethical Committee of Henan Provincial People's Hospital, People's Hospital of Zhengzhou University [approval no. (2020) No.147] on 19 October 2020.

Results

A total of 285 infants met the eligibility criteria. Forty-six infants developed PNAC, 33 of whom were matched with controls (Figure 1). The demographic and clinical characteristics related to

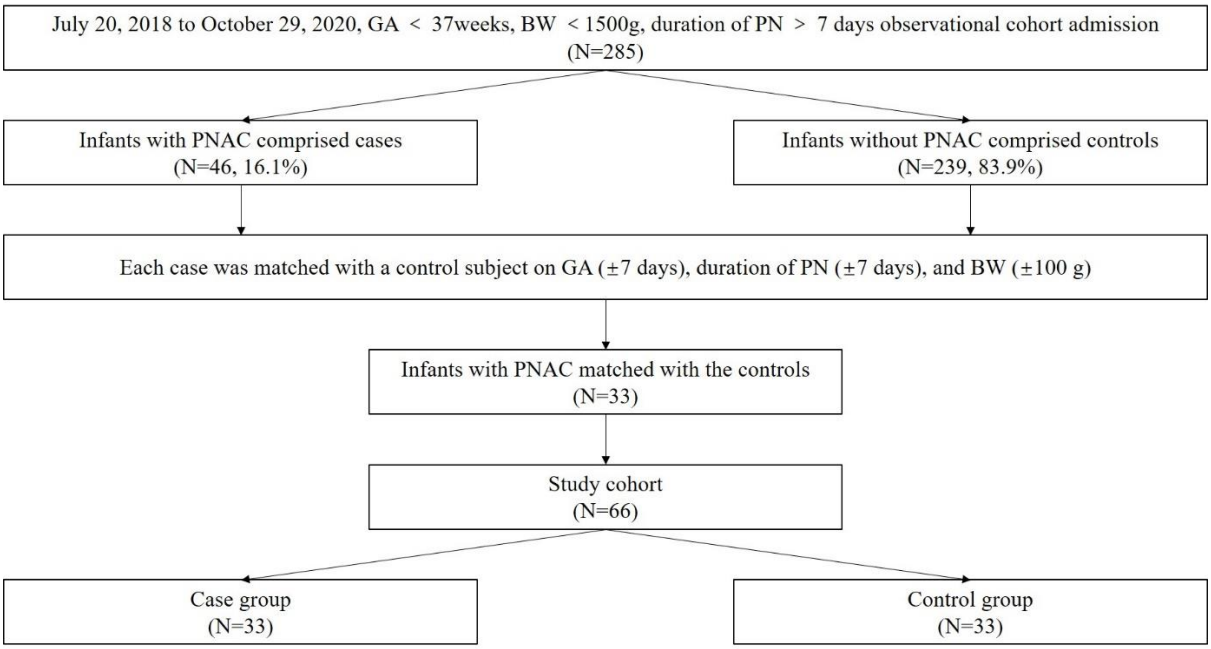

Figure 1. Flow chart of all preterm infants born with gestation age < 37 weeks, birth weight < 1500 g, duration of PN > 7 days during the study period. GA, gestation age. BW, birth weight. PN, parenteral nutrition. PNAC, parenteral nutrition-associated cholestasis

Table 1. Demographic characteristics of study participants

Variable	PNAC group (n = 33)	Non-PNAC group (n = 33)	*P*-value
Male, n (%)	23 (69.7)	20 (60.6)	0.606
Gestational age at birth, weeks	28.7 (27.6-29.7)	29.0 (27.6-29.6)	0.799
Cesarean section, n (%)	28 (84.8)	26 (78.8)	0.751
5-min Apgar score	9 (8-10)	9 (8-9)	0.380
Birth anthropometrics			
Weight, g	1050 (845-1220)	1070 (860-1170)	0.848
Length, cm	36 (33-38)	35 (32-37)	0.350
Head circumference, cm	26 (25-28)	26 (25-27)	0.494
Surgical conditions			0.509
Necrotizing enterocolitis, n (%)	2 (6.1)	0 (0.0)	
Intestinal atresia, n (%)	1 (3.0)	0 (0.0)	
Others [1], n (%)	3 (9.1)	3 (9.1)	
Sepsis, n (%)	4 (12.1)	4 (12.1)	1.000
Ventilators, days	8 (2-22)	9 (5.5-20)	0.941

PNAC, parenteral nutrition-associated cholestasis. [1] Others includes patent ductus arteriosus (PDA), congenital megacolon, incarcerated inguinal hernia, and anorectal fistula. Continuous variables are presented as median (interquartile).

PNAC are shown in Table 1. There was no significant difference between the PNAC group and non-PNAC group in terms of gender, GA, mode of delivery, 5-min Apgar score, birth anthropometrics (weight, length, and head circumference), surgical conditions, sepsis, and duration of ventilation.

Infants in the case group developed PNAC at the age of 29 (23-39) days. Liver function indices in the matched controls were analyzed at the corresponding age of 27 (20-39) days. Liver function tests at the onset of PNAC are shown in Table 2. ALT, AST, DBI, and TBA were significantly higher in infants with PNAC compared with infants without PNAC. There was no significant difference between groups with regard to AKP and GGT.

Characteristics of EN and PN support are shown in Table 3. There was no significant difference in days to start EN and episodes of EN interruption between the two groups. Before the onset of PNAC in the case group, though no statistically significant difference was observed in incremental feeding rate, daily average enteral intake, and daily average enteral energy, infants in the case group tended to have lower incremental

Table 2. Liver function tests at the onset of PNAC

Variable	PNAC group (n = 33)	Non-PNAC group [1] (n = 33)	P-value
ALT, U/L	12.3 (9.7-21.8)	9 (5.8-11.8)	0.007
AST, U/L	38.2 (29.5-60)	23.7 (19.7-28.5)	0.000
DBI, μmol/L	22.3 (19.3-33.3)	8.2 (5.5-10.4)	0.000
TBA, μmol/L	36.0 (19.0-49.4)	17.6 (9.6-26.4)	0.003
AKP, U/L	375 (259-489)	315 (230-462)	0.466
GGT, U/L	166 (77-282)	81 (39-171)	0.060

PNAC, parenteral nutrition-associated cholestasis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBI, direct bilirubin; TBA, total bile acid; AKP, alkaline phosphatase; GGT, γ-glutamyl transpeptidase. [1] Data in non-PNAC group were collected when PNAC occurred in the matched infants (case). Continuous variables are presented as median (interquartile).

Table 3. Characteristics of EN and PN support.

Variable	PNAC group (n = 33)	Non-PNAC group (n = 33)	*P*-value
Days to start EN, days	3 (2-4)	3 (2-4)	0.997
Incremental feeding rate [1], ml/kg/d	2.5 (0.9-4.3)	4.0 (2.6-5.3)	0.102
Daily average enteral intake [1], ml/kg/d	46 (15-77)	40 (28-82)	0.536
Daily average enteral energy [1], kcal/kg/d	35 (11-58)	30 (20-61)	0.698
Episodes of EN interruption before PNAC [2], n	0 (0-1)	0 (0-1)	0.266
Enteral intake [3], ml/kg	65 (13-149)	102 (41-161)	0.259
Enteral energy [3], kcal/kg	45 (9-111)	72 (31-118)	0.285
Duration of PN, days	35 (24.5-43.5)	36 (30-45.5)	0.363
Intravenous lipid emulsion [4]			0.375
MCL/LCT, n (%)	25 (78.1)	28 (84.9)	
SMOF, n (%)	3 (9.4)	4 (12.1)	
MCL/LCT + SMOF, n (%)	4 (12.5)	1 (3.0)	

EN, enteral nutrition; PN, parenteral nutrition; PNAC, parenteral nutrition-associated cholestasis; [1] before the onset of PNAC; [2] EN interruption was defined as enteral feeding interruption for a period exceeding 24 hours when EN > 20ml/kg; [3] at the onset of PNAC; [4] one infant in PNAC group received PN without lipid emulsion; MCT/LCT, medium-chain triglyceride/long-chain triglyceride (Fresenius Kabi, Wuxi, Jiangsu, China); SMOF, soybean oil (SO), medium-chain triglyceride (MCL), olive oil (OO) and fish oil (FO) (Fresenius Kabi, Wuxi, Jiangsu, China). Continuous variables are presented as median (interquartile).

feeding rates (2.5 ml/kg/d vs 4 ml/kg/d, p = 0.102). Enteral intake and enteral energy at the onset of PNAC were statistically similar. Equally, enteral intake and enteral energy seemed lower in the case group (65 ml/kg vs 102 ml/kg, p = 0.259; 45 kcal/kg vs 72 kcal/kg, p = 0.285; respectively). There was no significant difference in the duration of PN and intravenous lipid emulsions.

This study included 33 case-control pairs. Given the research objective, results of univariate analysis (Table 3), and clinical experience, four factors including incremental feeding rate, episodes of EN interruption, enteral intake, and enteral energy were selected for multivariate analysis using a conditional logistic regression model with the forward stepwise (likelihood ratio) method. The Omnibus test of model coefficients yielded the following results: -2Log Likelihood = 34.372; χ^2 = 9.331; p = 0.002. Incremental feeding rate entered the final model and was negatively related to PNAC (β = -0.735; odds ratio 0.479; 95% confidence interval 0.272-0.844; p = 0.011). We further attempted to include additional variables (NEC, sepsis, lipid emulsion type, and factors mentioned above) in the model using the same methodology. Incremental feeding rate remained the only variable that entered the equation, consistently demonstrating a negative association with PNAC (β = -0.735; odds ratio 0.479; 95% confidence interval 0.272-0.844; p = 0.011). In other words, even with an increase of 1 ml/kg/d in enteral feeding volume, the probability of PNAC will decrease by 52.1%.

Discussion

We conducted this single-center nested case-control study to explore the correlation of EN strategies with PNAC in preterm infants with birth weight less than 1500 g. The results showed that incremental feeding rate was negatively associated with PNAC. Even with an increase of 1 ml/kg/d in enteral feeding volume, the probability of PNAC will decrease by 52.1%.

Chinese Society of Parenteral and Enteral Nutrition (CSPEN) guidelines indicate that for preterm infants with a birth weight less than 1500 g, enteral feeding should start at 15-20 ml/kg/day and increase at a rate of 15-20 ml/kg/day (11). At our center, the incremental feeding rate is significantly lower than the recommended guidelines (2.5 ml/kg/day in the PNAC group and 4 ml/kg/day in the non-PNAC group). Factors affecting the feeding advancement rate include abdominal distension, vomiting, bowel sounds, gastric residual volume, and severe infections. Clinical experience may impact this professional judgment and decisions. Due to concerns about the occurrence of NEC, neonatal physicians are very cautious when increasing feeding volumes. This may explain why our incremental feeding rate is slower.

Though PNAC is usually defined as direct bilirubin > 2 mg/dL (1, 9, 16, 17), no consensus has yet been reached (4, 18, 19). Early detection of cholestatic jaundice and timely, accurate diagnosis are important for successful treatment and an optimal prognosis (14). We chose to define cholestasis as direct bilirubin ≥ 1.0 mg/dL with total bilirubin < 5.0 mg/dL or direct bilirubin > 20% of total bilirubin with total bilirubin > 5.0 mg/dL in order to distinguish true cholestasis from hyperbilirubinemia. In our study, the day of life at cholestasis diagnosis was 29 (23-39) days, which is shorter than in previous studies (9, 20). This may be explained by the different definitions chosen. Asymptomatic increase of aminotransferase frequently occurs within 2-3 weeks after starting PN and is often followed by an increase of serum DBI, AKP, GGT, and BA (8). We found that serum ALT, AST, DBI, and TBA levels of cholestatic infants at the onset of PNAC were higher than those of infants without cholestasis, but still within normal limits in this study. Hwang et al. revealed similar trends of ALT and AST at 1, 2, and 3 weeks after PN infusion in ELBW infants (21). However, ALT and AST are not reliable predictors of PNAC as previous studies reported (21, 22). Therefore, early detection of PNAC in preterm infants through DBI is still a widely used method in current clinical practice. The problem is that no consensus on the standard of diagnosis has yet been reached.

In our center, enteral nutrition was initiated as soon as possible after birth if applicable and increased as quickly as possible according to tolerance (23). Even so, days to start EN were 3 (2-4) days in both PNAC and non-PNAC groups, which is longer than in the latest studies (24-26). Guidelines for feeding VLBW infants suggested starting trophic feeds (defined as 10-15 ml/kg/day of milk feeds) preferably within 24 hours of life (27). In addition, a recent randomized controlled study revealed that early introduction of enteral feeds (on day 1 after birth) in stable VLBW infants resulted in the earlier achievement of full enteral feeding and did not increase the risk of necrotizing enterocolitis (NEC) (28). Therefore, the feeding regimen in our center did not strictly

follow the latest guideline and is relatively conservative from the point of view of the initiation of EN. Though we did not explore the relationship between days to start EN and incidence of PNAC on account of no statistical difference between case and control groups, minimization of PNAC requires early initiation of enteral feeding as soon as possible (29). We should make efforts to introduce EN earlier to optimize nutritional support in VLBW and ELBW infants.

In this study, the speed of increasing enteral feeding (2.5 ml/kg/d in the PNAC group; 4.0 ml/kg/d in the non-PNAC group) was much lower than in previous studies (23, 30). There remains a lack of consensus on the optimal feeding strategies for preterm infants (31, 32). Chinese Society of Parenteral and Enteral Nutrition (CSPEN) guidelines for nutrition in neonates have been used nationwide since their publication (11), which pointed out that for infants weighing < 1500 g, nutritional feeds should start at 10-20 ml/kg/day and increase by 15-20 ml/kg/day. Meanwhile, the guidelines indicated that the milk volume should be advanced according to feeding tolerance. Initiation and advancement of enteral feeding in very low birth weight infants remain a challenge because of acute illnesses in the early neonatal period and functional immaturity of the gastrointestinal system, which can lead to feeding intolerance (31). Previous randomized controlled trials, which evaluated the effect of slow (20 ml/kg/d or 15 ml/kg/d) or rapid (30 ml/kg/d or 35 ml/kg/d) rates of advancement of enteral feeding volumes on the clinical outcomes in preterm infants, were conducted in stable neonates (33, 34). Preterm infants in this study, who were admitted to the NICU immediately after birth, included not only stable neonates but also unstable ones. Due to acute illnesses or functional immaturity of the gastrointestinal system, feeding intolerance occurred often, which would affect feeding practice. Also, the EN increment rate (ml/kg/d) in this study was an average value of daily increment. The extraordinarily low EN increment rate, which was consistent with clinical practice, may be explained by the above two points. Meanwhile, we observed that two infants in the PNAC group (6.1%) experienced NEC and none in the non-PNAC group. It seems that faster enteral advancement does not cause a higher incidence of NEC. A recent randomized controlled study also showed that the speed of advancing enteral feeding volumes (daily increments of 30 ml/kg as compared with 18 ml/kg) did not affect the risk of NEC in very preterm or VLBW infants (23). We further concluded that even with an increase of 1 ml/kg/d in enteral feeding volume, the probability of PNAC will decrease by 52.1% through conditional logistic regression. In consideration of feeding strategies in our center, we believe that this conclusion is feasible to be used in practice and may bring clinical benefits.

Limitations

The limitations of this study include its single-center design and relatively small sample size. Future multicenter randomized controlled trials would provide more compelling evidence to further investigate the impact of enteral feeding advancement rates on the incidence of PNAC.

Conclusion

Incremental feeding rate may be associated with the development of PNAC in preterm infants. An adequate increase in incremental feeding rate may be useful in reducing the incidence of PNAC in preterm infants with birth weight less than 1500 g.

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Conflicts of interest

The authors declare that they have no competing interests.

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