Araştırma Makalesi / Research Article

Can inappropriate use of antibiotic prolong the length of hospital stay in acute gastroenteritis?

Uygunsuz antibiyotik kullanımı akut gastroenteritte hastanede kalış süresini uzatabilir mi?

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Abstract

Background: The aim of this study was to clinically evaluate the patients admitted to our hospital and treated with the diagnosis of AGE (acute gastroenteritis), and to investigate the treatment techniques administered to these patients before admitting to our hospital.

Material and Methods: The clinical records of the patients were retrospectively reviewed.

Results: 352 cases diagnosed with AGE were included in the study. 61.1% of the patients were male and 38.9% were female. The mean age of the patients was 14.8 ± 19.3 months. When the 244 patients with the diagnosis of AGE and without any comorbidity were divided into two groups and examined according to their use of oral antibiotics before admitting to our clinic, the length of hospital stay was significantly shorter in the group not used oral antibiotic than in the group used oral antibiotic ($p<0.001$). The mean healthcare costs were lower in the group not used oral antibiotic than in the group used oral antibiotic.

Conclusion: In cases with AGE, the mean length of hospital stay is not affected by gender, causative pathogen and presence of dehydration. It has been thought that the inappropriate use of antibiotic in the AGE treatment may increase the healthcare costs by prolonging the mean length of hospital stay.

Keywords: Antibiotics, gastroenteritis, length of stay, rotavirus

Özet

Amaç: Bu çalışmanın amacı hastanemize başvuran ve AGE (akut gastroenterit) tanısıyla tedavi edilen hastaları klinik olarak değerlendirmek ve hastanemize başvurmadan önce bu hastalara uygulanan tedavi yöntemlerini araştırmaktır.

Materyal ve Metod: Hastaların klinik kayıtları retrospektif olarak incelendi.

Bulgular: AGE tanısı alan 352 olgu çalışmaya alındı. Hastaların% 61,1'i erkek,% 38,9'u kadındı. Hastaların yaş ortalaması 14,8 ± 19,3 ay idi. AGE tanısı alan ve komorbiditesi bulunmayan 244 hasta kliniğimize başvurmadan önce oral antibiyotik kullanımlarına göre iki gruba ayrılılıp incelendiğinde, ortalama hastanede kalış süresi, oral antibiyotik kullanılmayan grupta oral antibiyotik kullanan gruba göre anlamlı olarak daha kısa bulundu ($p <0.001$). Oral antibiyotik kullanılmayan grupta ortalama sağlık hizmeti maliyetleri, oral antibiyotik kullanılan gruba göre daha düşüktü.

Sonuç: AGE'li olgularda, ortalama hastanede yatış süresinin uzunluğu cinsiyet, etken patojen ve dehidratasyon varlığından etkilenmemektedir. AGE tedavisinde uygunsuz antibiyotik kullanımının, hastanede kalış süresinin uzamasıyla birlikte sağlık hizmeti maliyetlerini artırabileceği düşünülmüştür.

Anahtar Kelimeler: Antibiyotikler, gastroenterit, yatış süresi, rotavirüs

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Introduction

Acute gastroenteritis (AGE) is an important disease caused by various bacteria, viruses and parasites in all humans, especially in children under five years of age. This condition continues to be one of the major causes of morbidity and mortality, especially in developing regions around the world (1,2). AGE is the most common cause of morbidity and mortality in children, following lower respiratory tract infection, and is also a major health issue for Turkey (3). Worldwide, diarrhea accounts for 8.6% of all deaths under the age of five (4). Gastrointestinal system infections are common in developing countries where the hygiene conditions and the health system are poor and where the infrastructure and sanitation for nutrients are inadequate (5). In our day, acute diarrhea has still been very common all over the world and causes serious problems, despite the decreased incidence and severity in developed countries (6).

AGE may arise at any age in the form of sporadic cases or epidemics, however, the etiologic agents and the disease severity vary by age. Only about 60-70% of the causes leading to acute diarrhea in children can be diagnosed and the majority of which are gastrointestinal infections (6). While viruses are common among the infectious agents (30-70%), the less rare causes include bacteria (10-20%) and parasites (5-10%) (3,6). The various viruses, which are the major cause for AGEs worldwide, include rotavirus, enteric adenoviruses (adenovirus 40, 41) and caliciviruses (norovirus and sapovirus). Astrovirus, coronavirus and bocavirus are other viral agents for infectious diarrhea in children, although it varies depending on the geographical region worldwide (7).

Although acute viral gastroenteritis often limits itself, it may sometimes lead to serious dehydration. Since there is no specific antiviral treatment other than proper fluid and electrolyte treatment, knowing that it frequently shows up in the clinic gives rise to the thought that unnecessary antibiotic use will also be avoided. Today, especially in developing countries, inappropriate use of antibiotics (IUA) can be seen in diseases such as acute bronchiolitis, acute otitis media and acute gastroenteritis (8,9). IUA can lead to adverse outcomes, increased costs, and antimicrobial resistance (9). In this study, it was aimed to examine the clinical course of the patients admitted to our hospital and treated with the diagnosis of AGE, and the treatment techniques administered to the patients until hospitalization.

Material and Methods

In this study, the patients, who treated due to AGE between the years of 2015-2016, were retrospectively investigated. 352 patients with AGE were included in the study. The socio-demographic characteristics of the patients, such as age and gender and geography they live in, have been recorded. The modified Vesikari score (MVS) was used while evaluating the clinical findings (Table 1). According to the scoring system, the scores of 0 to 8, 9 to 10, ≥11 points signified mild, moderate and severe disease, respectively (10). The severity of dehydration was also determined using the clinical dehydration scale (CDS) (11). According to the CDS, the values of <3%, 3 to 6%, >6% were evaluated as mild, moderate and severe dehydration, respectively (11,12). All patients had a history of using oral probiotic agents, oral rehydration fluid, and oral zinc supplementation therapy for at least 48 hours in their anamneses. According to the anamnestic data, it was determined that the probiotic types used were lactobacillus rhamnosus or saccharomyces boulardii. 244 patients without any comorbidity or evident pathologic finding other than AGE were examined by dividing into two groups according to the AGE treatments they used for at least 24 hours until admitting to our clinic; the group used oral antibiotherapy (OA) and the group not used oral antibiotherapy (non-OA). During the follow-up period, the oral antibiotherapies of all the patients without any comorbidity or evident pathologic finding other than AGE clinic, which were initiated in centers other than our clinic, had been discontinued. Oral rehydration therapy had been initiated as soon as possible for patients admitted to the hospital. Breastfeeding had not been interrupted in the breastfeeding patients. Intravenous fluid replacement therapy had been administered to the patients with poor oral intake in accordance with the dehydration rates. In the patients without any evident pathologic finding or comorbidity other than AGE clinic, no specific treatment had been administered except fluid replacement therapy. In accordance with World Health Organization guidelines, acute diarrhea in our study was defined as more than three watery stool within 24 hours or, as more frequent and more watery stool than normal in breastfeeding infants (13).

Table 1. Modified Vesikari Score (MVS)

Points	0	1	2	3
Diarrhea duration (hr)	0	1-96	97-120	≥ 121
Max no. of diarrheal stools/24 hr period (in the course of the disease)	0	1-3	4-5	≥ 6
Vomiting duration (hr)	0	1-24	25-48	≥ 49
Max no. of vomiting episodes/24 hr period (in the course of the disease)	0	1	2-4	≥ 5
Max recorded fever	< 37^{0}C	37.1-38.4^{0}C	38.5-38.9^{0}C	≥ 39^{0}C
Future healthcare visit	-	-	Primary Care	Emergency Dept.
Treatment	None	IV Rehydration	Hospitalization	-

Sampling and Analysis Techniques Used

All stool samples had been evaluated macroscopically and microscopically (native-lugol X400 magnification). In addition to these, the results of rotavirus, adenovirus and entamoeba histolytica antigen tests in stool culture and stool evaluated to determine the etiology of AGE were reached. The analyzed blood count results had been obtained by a hematology analyzer, Cell-Dyn Ruby (Abbott Diagnostics, Abbott Park, IL). The patients' electrolyte and C-reactive protein (CRP) values had been obtained by a spectrophotometric chemistry analyzer, Architect C16000 (Abbott Diagnostics, Abbott Park, IL).

Fresh stool samples (samples collected within one hour) had been used to detect the antigens. The samples taken had been delivered to the microbiology laboratory within about 10 minutes. The microscopic examination and viral antigen detection of the samples had been performed within 1 hour. The adenovirus and rotavirus analyses had been performed using immunochromatographic technique (Ameritek-USA one step rapid adenovirus / rotavirus complex 2-panel card test). The stool cultures had been studied especially for Salmonella and Shigella in the case of presence of leukocyte in the stool, concomitant fever, negative antigen tests, or presence of bloody diarrhea with mucus. Entamoeba Histolytica in stool had been determined by antigen detection (E. histolytica II; TechLab, Blacksburg, VA, USA), using ELISA technique. The treatment costs of the patients were retrospectively evaluated in Turkish Lira (TL). The statistical analysis was performed after converting the cost into the US dollar ($) currency based on the exchange rate of the Central Bank of the Republic of Turkey on 27.03.2018 (http://www.tcmb.gov.tr/kurlar/201803/27032018.xml) (1 $ = 3.97 TL).

Data Analysis

The statistical analyses were performed using the SPSS version 24.0 (SPSS Inc., Chicago, IL) software package. The descriptive statistics were summarized as number, percentage, mean and standard deviation. The visual (histogram and probability plots) and analytical techniques (Kolmogorov-Smirnov, Shapiro-Wilk tests) were used to evaluate whether the variables follow normal distribution. The numerical variables determined according to normal distribution were compared between two groups using the Independent-Samples T-Test, and between three groups using the One-Way ANOVA test. The homogeneity of the variables was evaluated by the Levene test. The post-hoc analyses were performed using the Bonferroni test in the cases of significant differences. The Pearson correlation test was used for correlation analyses. The Pearson Chi-square analysis was used to compare the ordinal data. In the study analyses, the comparisons with a probability (p) value smaller than 0.05 ($p<0.05$) were considered to be statistically significant.

Results

A total of 352 patients with AGE were included in the study. 25.3% of the patients had been admitted in 2015 and 74.7% were admitted in 2016. 61.1% of the patients were male and 38.9% were female. When the distribution of the patients was examined in terms of age ranges, 67.9% were between 0-12 months, 20.2% were between 13-24 months, 7.7% were between 25-60 months and 4.3% were older than 61 months of age (Table 2).

Table 2. Demographic characteristics of patients

Gender	0-12 month	13-24 month	25-60 month	>61 month	Total (n=352)
Male/n	149	47	14	5	215(61.1)
Female/n	90	24	13	10	137(38.9)
Total n(%)	239(67.9)	71(20.2)	27(7.7)	15(4.3)	352(100)
Rotavirus/n	90	29	5	1	125(35.5)
Adenovirus/n	18	4	0	0	22(6.3)
Entamoeba histolytica/n	47	9	7	6	69(19.6)
Unknown/n	84	29	15	8	136(38.6)
Total n(%)	239(67.9)	71(20.2)	27(7.7)	15(4.3)	352(100)

n: Number of cases

The most common complaint of the patients admitted with the diagnosis of AGE was diarrhea (92.3%). This was followed by the complaints of vomiting (67.8%), fever (35.8%), nausea (4.5%), bloody diarrhea (2.0%) and abdominal pain (1.1%). The patients had been clinically assessed in terms of dehydration. According to this, only 2.6% of the patients had no evidence of dehydration. 64.2% of the patients had mild, 31.8% had moderate and 1.4% had severe dehydration. The mean MVS in patients with no dehydration findings was 6.88 ± 0.78 points, the mean MVS in patients with mild dehydration findings was 8.73 ± 2.08 points, the mean MVS in patients with moderate dehydration findings was 10.65 ± 2.23 points and the mean MVS in patients with severe dehydration findings was 14.80 ± 1.09 points.

The stool macroscopy of the patients had been evaluated to be mucous in 53.2%, watery in 40.6%, bloody in 2.8% and only watery in 3.4%. The stool microscopy was normal in 44.6% of the patients, whereas erythrocyte had been identified in 15.3%, entamoeba histolytica cysts and / or trophozoite structures had been identified in 7.6%, fat cell had been identified in 10.2%, leukocyte had been identified in 11.5%, yeast cell had been identified in 7.6%, and both erythrocyte and leukocyte had been identified in 3.8%. No stool culture had been performed in 65.3% of the patients. The results of all stool cultures, especially evaluated in terms of salmonella and shigella, were negative.

Rotavirus antigen had been detected in 35.5% of the pa-

tients' stool samples, while entamoeba histolytica antigen had been detected in 19.6%(only 7.6% of the cases were visible on the gaita microscope) and adenovirus antigen had been detected in 6.3% (Table 2). None of the patients had a history of immunization against rotavirus. In 38.6% of the patients, the etiology could not be determined.

When the AGE agents determined by age groups were evaluated, the most common AGE agent was rotavirus in the age ranges of 0-12 months and 13-24 months, whereas the most common AGE agent was entamoeba histolytica in the age ranges of 25-60 months and >60 months (Table 2). Of the patients followed up with the AGE clinic, 69.3% had no additional comorbidity, 12.5% had respiratory, 9.7% had neurological, 4% had hepatobiliary, 2% had metabolic, 1.7% had urinary, 0.6% had hematologic, 0.3% had cardiac comorbidities.

The length of the hospital stay was not affected by the gender of the patients and the presence of dehydration (Table 3). Likewise, the etiological cause of AGE was not effective on the length of hospital stay (Table 3). The mean length of hospital stay was 6.9 ± 3.9 days in the AGE patients with comorbidity, while the mean length of hospital stay was 5.0 ± 2.6 days in AGE patients without any comorbidity. The mean length of hospital stay was significantly longer in those with a comorbidity than in those without comorbidity (Table 3).

Table 3. Relationships between duration of hospital stay and categorical variables

Hospitalization time / day		Mean±SD	p value
Gender*	Male	5.6± 3.1	0.474
	Female	5.2±2.3	
Dehydration*	No	5.4±4.1	0.256
	Yes	6.2±3.7	
Additional disease*	No	5.0±2.6	<0.001
	Yes	6.9±3.9	
Agent of AGE**	Unknown	5.9±3.0	0.979
	E. histolytica	5.8±2.8	
	Rotavirus	6.0±3.0	
	Adenovirus	5.4±3.3	

*:Student's t-test; **:One-Way ANOVA test; SD: Standard deviation; AGE: Acute gastroenteritis;E. Histolytica: Entamoeba histolytica

244 patients without any comorbidity or evident pathologic finding other than AGE were examined by dividing into two groups in terms of treatment technique administered before admission; the group used oral antibiotherapy (OA) and the group not used oral antibiotherapy (non-OA). 47.1% of the patients had stated in their anamnesis that they used oral antibiotics after the complaint of diarrhea has started, whereas 52.9% had stated in their anamnesis that they did not use any oral antibiotherapy. (Table 5). The most common oral antibiotic types used by the patients before admission were metronidazole (25.8%), amoxicillin/clavunate (22.5%) and cefuroxime/axetil (14.7%), respectively (Table 4).

Table 4. The type of oral antibiotics used by patients with an accompanying disease and no pathological finding other than AGE

Types of oral antibiotics used	n(%) (n=115)	Hospitalization time / day (mean±SD)	*p value
Benzyl Phenoxymethyl Penicillin	8 (7)	5.75±3.19	0.951
Ampicillin / sulbactam	8 (7)	6.0±1.85	
Amoxicillin / clavulanate	23 (20)	5.56±2.64	
Clarithromycin	6 (5.2)	5.50±2.88	
Cefixime	11 (9.6)	6.0±4.49	
Cefuroxime / axetile	8 (7)	5.87±2.03	
Cefaclor	7 (6.1)	5.85±2.19	
Cephalexin	8 (7)	5.87±5.08	
Metronidazole	36 (31.3)	5.83±3.97	

* One way anova test was performed; SD: Standard deviation

The mean MVS scores and mean ages of the group OA and the group non-OA were found to be similar (p=0.572) (Table 5). The distributions of AGE agents, probiotics species and gender for the OA group and non-OA group was similar. (Table 5). When the distribution of dehydration rates was examined in the groups, it was found that the patients with moderate-severe dehydration were more common in the non-OA group than in the OA group (Table 5) (p=0.028). When the laboratory tests of these two groups were examined, there was no significant difference between the mean values of sodium, potassium, urea and creatinine, whereas the mean value of white blood cell was significantly higher in the non-OA group and the mean value of CRP was significantly higher in the OA group (Table 5). In patients admitted to the hospital (n=244), there had been no additional complication or adverse outcome other than dehydration clinic. In all cases (n= 244), the need for follow up under intensive care conditions did not develop. The mean length of hospital stay was 4.41±1.50 days in the non-OA group, while the mean length of hospital stay was 5.79±3.35 days in the OA group (Table 5). The mean length of hospital stay was significantly shorter in the non-OA group than in the OA group (p<0.001) (Table 5). When the healthcare costs of the groups were compared, the mean healthcare cost was 133.32±45.59 $ in the non-OA group, whereas it was 175.05±101.56 $ in the OA group. When the two groups were compared, the mean healthcare cost was found to be significantly lower in the non-OA group than in the OA group (Table 5).

Table 5. Comparison of treatment groups

	Group using oral antibiotics (n=115)	Group not using oral antibiotics(n=129)	p value
Gender (Male/Female)	70/45	82/47	**0.664
Mean Age(month) ***	15.11±16.22	12.48±10.32	*0.139
Length of stay / day***	5.79±3.35	4.41±1.50	*<0.001
Healthcare costs / $***	175.05±101.56	133.32±45.59	*<0.001
Patients using *Lactobacillus rhamnosus* n(%)	61(25)	61(25)	**0.369
Patients using *Saccharomyces boulardii* n(%)	54(22.1)	68(27.9)	
Modified Vesikari Score / points***	9.45±2.46	9.57±2.36	*0.572
No dehydration- Mild dehydration n(%)	84(34.4)	77(31.6)	**0.028
Moderate-Severe dehydration n(%)	31(12.7)	52(21.3)	
Rotavirus n(%)	41(16.8)	47 (19.3)	**0.899
Adenovirus n(%)	7(2.9)	6(2.5)	**0.618
Entemoeba histolytica n(%)	26(10.7)	31(12.7)	**0.793
Unknown agent n(%)	41(16.8)	45(18.5)	**0.799
Public health center n(%)	35(14.3)	86(35.2)	**<0.0001
Private health center n(%)	80(32.8)	43(17.6)	
WBC (10^3/µL)***	12.11±41.77	13.69±5.18	*0.033
CRP (mg/dL)***	4.20±10.49	0.55±1.40	*<0.001
Urea (mg/dL)***	35.21±6.94	36.15±7.15	*0.315
Creatinine (mg/dl)***	0.42±0.33	0.39±0.09	0.161
Na (mmol/L)***	136.32±4.42	136.78±4.92	0.751
K (mmol/L)***	4.08±0.55	3.98±0.61	0.102

* Student t test; **:Pearson ki-square test; SD:Standard deviation; ***:Mean±SD; WBC:White blood cell; CRP: C-reactive-protein; Na:Sodium; K:Potassium; $: American dollars

When the mean length of hospital stay was evaluated according to the types of antibiotics used, the difference between the groups was not significant (p=0.951) (Table 5). The rate of admitting to public health institutions was 66.7% in the non-OA group patients without any underlying disease or evident pathologic finding other than AGE, while this rate was 30.4% in the OA group. When the frequency of admitting to private health institutions was compared for the OA group and non-OA group, it was found that the OA group were more frequently admitted to private health institutions (p<0.0001) (Table 5).

Discussion

AGEs seen in children are one of the public health problems that still has not lost its significance worldwide. Viruses are considered as an important cause of severe AGE, especially in children. Rotavirus can be prevented by vaccination and is the main cause of diarrhea-related deaths in children under the age of five (14). In our study, 352 gastroenteritis cases were evaluated and the most common agent was viruses with 39%. The most common agent among viruses was rotavirus with 35.5%. There was no history of rotavirus vaccination in any of the cases. The low rates of rotavirus vaccination in our study can be explained by the absence of rotavirus vaccination in the national immunization program between 2015-2016. It is seen that the incidence of viral gastroenteritis in Turkey varies depending on the regions (15). Nevertheless, the incidence of norovirus and astrovirus could not be assessed since the assessment of norovirus and astrovirus antigen is not routinely performed in the clinical practice of our hospital. In 61.4% of the cases, the agent could be determined. When various studies conducted in Turkey are examined, it is seen that the detection rate of agent in AGEs varies between 30-65% (15,16). It has been thought that the geographical region differences, as well as the use of different techniques in the agent isolation, such as PCR (polymerase chain reaction), may be influential on such a wide range (3,16,17).

The southeastern region of Anatolia ranks first in the regional distribution of intestinal parasites in Turkey (18,19). Because of that, in childhood gastroenteritis, entamoeba shows up to be the more common agent in Sanliurfa province than in other regions. Among all age groups, entemoeba had been isolated as the agent with a rate of 19.6%. Poor sanitation, lack of safe drinking water, improper practices in preparing food, and inadequate hygiene conditions pose a risk for protozoa-induced gastroenteritis (19). Over time, the safe drinking water supply and improvement of hygiene conditions in Sanliurfa province was considered as the possible causes of reduction in the incidence of entamoeba-related infection.

In our study, it was seen that the mean length of hospital stay for patients with AGE was not affected by gender, causative pathogen, presence of dehydration. However, the presence of a comorbidity and an evident pathological finding other than AGE significantly prolonged the mean length of hospital stay (Table 3). When the patients without any comorbidity or evident pathological finding other than AGE were divided into two groups according to whether they used oral antibiotics or not, and their mean length of hospital were examined, the difference was significant between the groups. Although the mean MVS score distributions of the groups were similar, it was seen that the cases of moderate and severe dehydration were more frequent in the non-OA group than in the OA group. In contrast to what was expected in the non-OA group where moderate-to-severe dehydration events occurred at a higher rate, the mean length of hospital stay was shorter. The mean values of sodium, potassium, urea and creatinine of the groups were similar. However, the fact that the mean values of CRP were significantly higher in the OA group than in the non-OA group, suggesting that it might be influential in selecting doctors who prefer oral antibiotics in the treatment of AGE. Nonetheless, CRP and procalci-

tonin are the biomarkers which are not routinely recommended, do not alter the treatment administered and have a low value of evidence in differentiating bacteria from non-bacterial etiology in AGE (12). In our study, it was considered that the healthcare costs increased due to the prolonged length of hospital stay. As a matter of fact, when the mean treatment costs of the OA group and the non-OA group were compared, the mean healthcare costs of the non-OA group have been found to be significantly lower. Furthermore, as a limitation of our study, the labor loss of the parents accompanying pediatric patients and the oral antibiotherapy itself were not analyzed in terms of cost burden, but it was considered that these conditions could cause an additional cost.

The IUA for childhood respiratory infections, AGEs, and subfebrile fever due to viral infections contributes to the development of resistance to antibiotics (20,21). According to management rules for AGE, antibiotic treatment should not be given to the majority of children unless specific conditions are present (12). Even in cases of proven bacterial gastroenteritis, antibiotherapy is not routinely needed. Antibiotherapy should be considered in AGE only for specific pathogens or in defined specific clinical conditions (12,22).

The rate of antibiotic use in AGE was found to be 47.1% in the patient records that we could reach in our study. Given the IUA in AGEs worldwide, this rate varies between 23-51% (23,24). In a study conducted in India, the antibiotic use in AGE has been found to be 71% and it has been indicated that occupational development programs could be useful to reduce these rates (24). Another study conducted in India has indicated that the IUA in AGEs was lower in public health facilities (23%) than in private clinics (51%) (23). In our study, it was seen that the OA group patients without any comorbidity or evident pathological finding other than AGE were more frequently admitted to private healthcare institutions compared with the non-OA group patients.

Gut microbiota has multiple beneficial functions for the host (25). These functions include numerous beneficial functions such as conversion of bile acids, synthesis of B and K group vitamins, and immune system modulation (26,27). It is considered that the IUA may have negative effects on the gut microbiota; the reduced microbiota diversity, especially in viral gastroenteritis, may restrict the ability of the intestinal flora to perform these beneficial functions by further adversely affecting the microbiota diversity (26,27).

Conclusion

This study is important in terms of containing current data on childhood AGEs in a developing country and being the first study investigating the relationship between cost-length of hospital stay together. The mean length of hospital stay is prolonged and an additional cost is incurred due to IUA in the AGE treatment. It was thought that more extensive studies on the IUA in AGE at different clinics of developing countries might be useful.

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