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ORIGINAL ARTICLE

Basic Study

Proton pump inhibitors increase the severity of hepatic encephalopathy in cirrhotic patients

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Author contributions: Fasullo M designed the study and wrote the manuscript; Rau P, Liu DQ and Holzwanger E helped edit the paper and assisted with statistical analysis; Mathew JP and Guilarte-Walker Y assisted with data collection and defining the patient population; Szabo G was the senior author, provided concepts and oversight for the study design, data acquisition, interpretation and editing of the manuscript.

Institutional review board statement: The study was reviewed and approved by the University of Massachusetts Medical School Institutional Review Board Approved Protocol (H00012102).

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Abstract

BACKGROUND

Liver cirrhosis is the late stage of hepatic fibrosis and is characterized by portal hypertension that can clinically lead to decompensation in the form of ascites, esophageal/gastric varices or encephalopathy. The most common sequelae associated with liver cirrhosis are neurologic and neuropsychiatric impairments labeled as hepatic encephalopathy (HE). Well established triggers for HE include infection, gastrointestinal bleeding, constipation, and medications. Alterations to the gut microbiome is one of the leading ammonia producers in the body, and therefore may make patients more susceptible to HE.

AIM

To investigate the relationship between the use of proton pump inhibitors (PPIs) and HE in patients with cirrhosis.

METHODS

This is a single center, retrospective analysis. Patients were included in the study with an admitting diagnosis of HE. The degree of HE was determined from subjective and objective portions of hospital admission notes using the West Haven Criteria. The primary outcome of the study was to evaluate the grade of HE in PPI users *versus* non-users at admission to the hospital and throughout their hospital course. Secondary outcomes included rate of infection, gastrointestinal bleeding within the last 12 mo, mean ammonia level, and model for end-stage liver disease scores at admission.

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RESULTS

The HE grade at admission using the West Haven Criteria was 2.3 in the PPI group compared to 1.7 in the PPI nonuser group (P = 0.001). The average length of hospital stay in PPI group was 8.3 d compared to 6.5 d in PPI nonusers (P = 0.046). Twenty-seven (31.8%) patients in the PPI user group required an Intensive Care Unit admission during their hospital course compared to 6 in the PPI nonuser group (16.7%) (P = 0.138). Finally, 10 (11.8%) patients in the PPI group expired during their hospital stay compared to 1 in the PPI nonuser group (2.8%) (P = 0.220).

CONCLUSION

Chronic PPI use in cirrhotic patients is associated with significantly higher average West Haven Criteria for HE compared to patients that do not use PPIs.

Key words: Cirrhosis; Hepatic encephalopathy; Proton pump inhibitors; Hepatology; Proton pump inhibitor

Core tip: In this study, we investigate whether proton pump inhibitor (PPI) use in hepatic encephalopathy patients predisposes them to more severe stages of hepatic encephalopathy as per West Haven Criteria. We found that chronic PPI use in cirrhotic patients is associated with significantly higher average West Haven Criteria for hepatic encephalopathy compared to patients that did not use PPIs. Our data also indicated that cirrhotic patients on PPIs have longer hospital stays, with increased morbidity and mortality during their hospital stays.

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INTRODUCTION

Liver cirrhosis is a late stage of hepatic fibrosis and is characterized by portal hypertension that can clinically lead to decompensation in the form of ascites, esophageal/gastric varices or encephalopathy. There are multiple etiologies of liver cirrhosis, with Hepatitis C, alcoholic hepatitis/alcoholic liver disease and non-alcoholic fatty liver disease being the most common causes in the developed world[1]. Some of the most common sequelae associated with liver cirrhosis are neurologic and neuropsychiatric impairments labeled as hepatic encephalopathy (HE). Neuropsychiatric changes associated with liver disease were first described by Adams and Foley in the 1940s and 1950s[2]. Since then, our understanding of what HE entails and what precipitates it has only marginally grown. According to the currently accepted definition, HE is a neuropsychiatric disorder that can encompass a broad spectrum of presentations summarized in the West Haven Criteria Severity Scale. HE spans from minimal to Grade I (mild confusion, disordered sleep), through Grades II (lethargy, moderate confusion), III (marked confusion, incoherent speech) and finally Grade IV (coma)[3,4].

While liver cirrhosis can predispose a patient to HE, there are additional triggers that can precipitate it or worsen its severity. Well established triggers include infection, gastrointestinal (GI) bleeding, constipation, and medications such as opioids and benzodiazepines[5-8]. New studies have cited other etiologies, including changes in gut flora and small bowel bacterial overgrowth[9,10]. More recently, there have been studies on the role of proton pump inhibitors (PPIs) in contributing to HE in cirrhotic patients. PPIs are commonly prescribed for many GI diseases, most commonly gastroesophageal reflux disease (commonly known as GERD), peptic ulcer disease, and gastritis[11]. In contrast to previous beliefs, recent data suggests that PPIs have the potential for multiple adverse effects. PPIs act by decreasing gastric acid secretion, which is believed to be protective against acid-related mucosal injury in the

stomach[12]. It was thought that their ability to protect the GI mucosa would mitigate the number of GI bleeds in cirrhotic patients, therefore reducing their risk of HE. However, new studies show that in addition to their direct effects in the stomach, PPIs may affect composition of the gut microbiome while also promoting small bowel bacterial overgrowth[13].

Normally, nitrogenous compounds formed by the gut are drained into the portal system and filtered by the liver[14]. These compounds then enter the urea cycle and are excreted in urine. However, in patients with liver disease, ammonia clearance is compromised due to reduced liver function and increased portosystemic shunting, leading to high levels of ammonia in the blood stream. When ammonia reaches the brain, it is metabolized by astrocytes and transformed from glutamate to glutamine *via* glutamine synthase. Accumulation of glutamine increases intracellular oncotic pressure, leading to cerebral edema. In patients with chronic liver disease, this cerebral edema can be subtle, and at this time, the edema alone does not explain all the findings of HE[15-17]. However, the morphological changes seen with astrocyte swelling are similar to the changes seen in Type II Alzheimer's disease[18]. Therefore, given the current mechanisms, it appears that ammonia levels (and subsequently astrocyte glutamine levels) have an overall neurotoxic effect.

Studies have shown that an increased gastric pH allows for increased gut microflora. In turn this can lead to increased bacterial translocation. Microflora species such as *Salmonella*, *Campylobacter jejuni, Escherichia coli*, *Clostridium difficile*, *Vibrio cholerae* and *Listeria* all appear to proliferate in high gastric pH[13]. In addition, the literature suggests that more severe bacterial proliferation such as small intestinal bacterial overgrowth has also been linked with gastric hypochlorhydria secondary to prolonged PPI use. Overall, it does appear that elevation of gastric pH allows for greater gut bacterial proliferation. Increased proliferation is not without consequence, as the gut microbiome is one of the leading ammonia producers in the body, and therefore may make patients more susceptible to HE, which is what we believe to be the driving force behind our findings. This would partly explain why rifaximin, a poorly absorbable synthetic antibiotic, can lower the risk of HE in cirrhotic patients by affecting the gut microbiota. Given that changes in gut flora may lead to worse HE, the role of PPIs must be reconsidered. This study investigates whether PPI use in HE patients predisposes them to more severe stages of HE as per the West Haven Criteria.

MATERIALS AND METHODS

Patient selection

This retrospective medical chart review was conducted at the UMass Memorial Medical Center. Records for patients who presented with acute HE between January 1, 2012 and January 1, 2016 were reviewed. Patients were included in the study with an admitting diagnosis of HE with and without coma with ICD-9 code 572.2 and ICD-10 codes K72.00 and K72.01.

Eligible patients were ≥ 18 years of age, had prior history of End Stage Liver Disease or cirrhosis as determined by consistent image findings and/or liver biopsy. Patients were on PPIs for a minimum of 30 d prior to hospital admission. Exclusion criteria included pregnancy, current prisoner, failure to sign consent, and concomitant diagnosis of human immunodeficiency virus.

Data collection

Utilizing medical record and data from Electronic Health Records, demographics (age, sex), grade of HE, Model End Stage Liver Disease (MELD) score, Length of stay, etiology of cirrhosis, concomitant infection, ammonia level, history of bleeding in the last 12 mo, etiology of HE, intensive care unit (ICU) stay, and patient expiration, were collected. The degree of HE was determined from subjective and objective portions of hospital admission notes using the West Haven Criteria. Grade I included lack of trivial awareness, presence of euphoria and/or anxiety, shortened attention span and/or altered sleep rhythm. Patients met Grade II if they were lethargic, had personality changes, disorientation to time, dyspraxia and/or asterixis on physical exam. Grade III encephalopathy included confusion, disorientation to space, somnolence or signs of semi-stupor. Finally, Grade IV was defined as coma. The institutional review board at UMass Medical School/UMass Memorial Medical Center approved this study.

Definition of events and study outcomes

The primary outcome of the study was to evaluate the grade of HE in PPI users *versus*

non-users at the time of admission to the hospital and throughout their hospital course. Secondary outcomes included rate of infection, GI bleeding within the last 12 mo, mean ammonia level, and MELD scores at admission.

Statistical analysis

Data was analyzed using R version 3.3.2 GUI 1.68 Mavericks built for Mac computer. The statistical significance of between-cohort differences in categorical variables was tested using the chi-square test and in continuous variables using the two-sample t-test. All tests were two-tailed with a significance level of $P < 0.05$. Multivariate analysis using a linear regression model was applied to primary and secondary endpoints to determine statistically significant differences between PPI users and non-users. The threshold for statistical significance was set at P values < 0.05.

RESULTS

Demographics and clinical characteristics

A total of 103 patients were included in this study from UMass Memorial Medical Center between January 2013 and December 2016. All patients had been diagnosed with liver cirrhosis based on imaging studies (U/S, computer scanning or magnetic resonance imaging) or liver biopsy and evidence of portal hypertension based on clinical signs, imaging or portal pressure measurement. Seventy-five (73%) of these cirrhosis patients were taking PPIs (PPI user), while twenty-eight (27%) patients with cirrhosis were not taking PPIs prior to enrollment (PPI non-user). The mean age of patients included in this study was 58.3 years, with the PPI user group being 59.6 years and in the PPI nonuser group being 55.3 years ($P = 0.044$). With regards to gender, males represented 54 (63.5%) patients in the PPI user group and 17 (47.2%) in PPI nonuser group ($P = 0.143$). Sixty-three (74.1%) patients were on lactulose in the PPI user group compared to 9 (80%) in the PPI nonuser group ($P = 0.599$).

Primary outcomes

The primary outcomes of this study were the grade of HE and hospital course for PPI users compared to non-users. The grade of HE using the West Haven Criteria was 2.3 in the PPI group compared to 1.7 in the PPI nonuser group, which represented a statistically significant difference ($P = 0.001$) (Table 1). With regards to hospital course, several outcomes were analyzed. The average length of hospital stay in the PPI group was 8.3 d compared to 6.5 d in PPI nonusers ($P = 0.046$). Twenty-seven patients (31.8%) in the PPI user group required an ICU admission during their hospital course compared to 6 in the PPI nonuser group (16.7%) ($P = 0.138$). Finally, 10 (11.8%) patients in the PPI group expired during their hospital stay compared to 1 in the PPI nonuser group (2.8%) ($P = 0.220$).

Secondary outcomes

Several secondary outcomes including infections, serum ammonia levels, MELD and GI bleeding were measured to further determine the effects of long-term PPI use in the cirrhotic population. With regards to infections, 5 patients (5.9%) in the PPI group developed *Clostridium difficile* compared to 0 in the PPI nonuser group (0%) ($P = 0.324$). Ten patients (11.8%) of the PPI group developed pneumonia compared to 1 in the PPI nonuser group (2.8%) ($P = 0.220$). Five patients in the PPI group developed spontaneous bacterial peritonitis compared to 4 in the PPI nonuser group (11.1%) ($P = 0.533$). The mean ammonia level of the PPI group on admission to the hospital was significantly higher, 67.8 mg/dL compared to 45.5 mg/dL in the PPI non-user group ($P = 0.095$). The mean MELD for the PPI group was 19.7 compared to 20.3 in the PPI nonuser group ($P = 0.687$). Twenty-six patients (30.6%) in the PPI group were admitted to the hospital for a GI bleed within the year prior to admission compared to 13 (36%) in the PPI nonuser group ($P = 0.703$) (Table 2).

Linear regression model

The multiple linear regression models showed that PPI use was associated with a higher grade of HE in cirrhosis compared to no PPI use. After adjustment for age, sex, MELD score, and lactulose use, the association between PPI use and HE grade was maintained ($P < 0.001$), with a beta of 0.607 and standard error of 0.179. In addition, a higher MELD score was also associated with a higher HE grade, with a beta of 0.024 and standard error of 0.011 ($P = 0.041$) (Table 3).

DISCUSSION

Table 1 Grade of hepatic encephalopathy in proton pump inhibitor users *versus* nonusers

Grade of HE	PPI user	PPI nonuser
	n = 75	*n* = 28
Grade 1	15 (20.0)	11 (39.3)
Grade 2	32 (46.6)	13 (46.4)
Grade 3	18 (24.0)	4 (14.3)
Grade 4	10 (13.4)	0 (0)

n (%), Grade of hepatic encephalopathy (HE) is defined by the West Haven Criteria Severity Scale for HE: Grade I (mild confusion, disordered sleep), II (lethargy moderate confusion), III (marked confusion, incoherent speech), IV (coma). HE: Hepatic encephalopathy; PPI: Proton pump inhibitor.

Because of their effectiveness in suppressing gastric acid secretions, PPIs have become one of the most commonly prescribed drug classes with annual expenditures in 2009 estimated at $13 billion in the United States and $24 billion worldwide[19]. The first PPI available was omeprazole [Prilosec, Prilosec OTC, Zegerid, Zegerid OTC Losec in Canada], which served as a basis for all other PPIs in its mechanism of action by causing irreversible inhibition of H^+/K^+ ATPase, therefore halting hydrogen ion expulsion into the gastric lumen. While many studies have confirmed PPIs to be safe, our study indicates that in cirrhosis patients, the use of PPIs is associated with worsened hospital outcomes.

In this study, we found that hospitalized cirrhotic patients on a PPI had a significantly higher average West Haven Criteria for HE (score of 2.3) compared to patients who were not on a PPI (scored an average of 1.7, $P = 0.001$). Using linear regression models, we showed that patients using PPIs had a higher West Haven Criteria grade HE regardless of age, sex, MELD score, and/or lactulose use. Other statistically significant differences between the PPI user and non-user groups included longer length of hospital stay (8.5 d for PPI users *vs* 6.5 for PPI nonusers, $P = 0.046$). In alignment with patients having a higher grade of HE as well as a longer length of hospital stay, a greater percentage of patients in the PPI user group also had an ICU admission, indicating the greater extent of systemic involvement in this group. A recent meta-analysis by Bian *et al*[20] supports our contention that there is a higher risk of developing HE in PPI users with liver dysfunction.

Prior studies have also indicated that PPI use could worsen HE in cirrhotic patients. A dose response analysis by Tsai *et al*[21] stratified patients based on length of PPI use and showed that longer PPI use led to higher rates of HE. The result remained statistically significant after adjustment of patient comorbidities. Hung *et al*[22] showed that cirrhotic patients on a PPI with HE had higher mortality rates at 30 d, 90 d and one year compared to cirrhotic patients with HE not on PPIs. This study investigates whether PPI use in HE patients predisposes them to more severe stages of HE as defined by the West Haven Criteria. Our analysis shows that patients on a PPI had significantly higher West Haven Criteria scale episode of HE compared to those not on a PPI (2.3 *vs* 1.7, $P = 0.001$). In addition, our study shows that PPIs predispose cirrhotic patients towards worsened encephalopathy regardless of age, sex, MELD score, or lactulose use.

The exact pathophysiology of HE is still not fully understood. Multiple mechanisms of action have been hypothesized and investigated, including the role of ammonia, increased GABA receptors in the brain, and accumulation of endogenous opioids[23]. Overall, it appears that HE is multifactorial, with accumulation of ammonia being a leading cause of overt HE[24]. In fact, studies have shown that HE ammonia levels are increased in 90% of patients. The primary source of ammonia in the body is the GI tract as a byproduct of chronic bacterial colonization, by enterocytes as they transform glutamine into ammonia, and by *H. pylori*, which metabolizes urea into ammonia. However, *H. pylori*'s role in HE is still unclear[25,26].

One of the secondary endpoints in this study was determining the risk for infection in patients with cirrhosis on a PPI. Our data shows that patients on a PPI may have higher rates of *C. difficile* infection, pneumonia and spontaneous bacterial peritonitis. However, these results were not statistically significant with *P*-values of 0.324, 0.220 and 0.533, respectively. This is thought to be due to this study's small sample size of 103 patients. A recent meta-analysis by Lambert *et al*[27] again demonstrated the association of community acquired pneumonia and *Clostridium difficile*-associated diarrhea (CDAD) with the use of PPI. The most likely pathogenesis of the development of these infections has been attributed to direct acid suppression in the

Table 2 Participant characteristics

Variables	Total, *n* = 103	PPI user, *n* = 75	PPI nonuser, *n* = 28	*P* value
Age, yr, Mean ± SD	58.3 (10.8)	59.6 (10.6)	55.3 (10.7)	0.044[a]
Sex, male, *n* (%)	71 (58.7)	54 (63.5)	17 (47.2)	0.143
On lactulose, *n* (%)	92 (76)	63 (74.1)	29 (80)	0.599
Bleeding in last 12 mo, *n* (%)	39 (32.2)	26 (30.6)	13 (36.1)	0.703
Infection, *n* (%)				
Clostridium difficile colitis	5 (4.1)	5 (5.9)	0 (0)	0.324
Pneumonia	11 (9.1)	10 (11.8)	1 (2.8)	0.220
Spontaneous bacterial peritonitis	9 (7.4)	5 (5.9)	4 (11.1)	0.533
Serum ammonia level, Mean ± SD	61.1 (67.2)	67.8 (67.8)	45.5 (64.2)	0.095
Grade of hepatic encephalopathy, Mean ± SD	2.1 (0.9)	2.3 (0.9)	1.7 (0.7)	0.001[b]
MELD score, Mean ± SD	19.9 (7.2)	19.7 (7.4)	20.3 (6.7)	0.687
Length of stay in d, Mean ± SD	8.5 (7.0)	8.3 (7.9)	6.5 (3.7)	0.046[a]
Required ICU, *n* (%)	33 (27.3)	27 (31.8)	6 (16.7)	0.138
Expired, *n* (%)	11 (9.1)	10 (11.8)	1 (2.8)	0.220

[a]$P < 0.05$,
[b]$P < 0.01$. MELD: Model for end-stage liver disease; ICU: Intensive care unit.

stomach and small bowel. With regards to CDAD, Janarthanan *et al*[28] suggested that the alkaline status of the stomach (pH > 5) likely predisposes the patient to enhanced survival of *C. difficile* vegetative spores. A recent study in 2018 by Naito *et al*[29] confirms our notion that continued PPI use leads to intestinal dysbiosis. Using 16S rRNA gene sequencing, PPIs were found to significantly increase certain enteric microbe taxonomy, including *Streptococcaceae* and *Enterococcaceae*, which are risk factors for CDAD, and to decrease *Faecalibacterium*, a commensal anti-inflammatory microbe present in human models.

Our paper has several limitations. First, because it is a retrospective review, information collection is incomplete, particularly regarding follow-up evaluation. Secondly because, we had an uneven distribution of the number of patients in the PPI use and non-use groups. Finally, due to the small sample size used for our study, several of our secondary outcomes were not statistically significant, including several infections and ICU admission rate, likely secondary to a lack of power. Again, as with any retrospective study, it is important to note that this type of study is unable to define exact causality. Further randomized, controlled, prospective studies are needed to help confirm the observation seen in our study.

In conclusion, PPIs are commonly prescribed for many GI diseases including GERD, peptic ulcer disease, and gastritis. They are often used without regard for their adverse effects. Our study demonstrates that PPI use in cirrhotic patients is associated with more severe degree of HE compared to those not on a PPI. Our data also showed that PPI use in this population was associated with a longer hospital stay and higher percentage of patients requiring an ICU admission. We suggest reducing PPI use in the cirrhotic population as a means to reduce episodes of HE. Further randomized-controlled, prospective studies are needed to help confirm this observation.

Table 3 Linear regression models, grade of hepatic encephalopathy

Variables	B ± SE	*P* value
Model 1, demographic variables		
Age	-0.001 ± 0.001	0.871
Sex	0.062 ± 0.167	0.710
PPI use	0.607 ± 0.180	0.001[b]
Model 2, medical comorbidities		
Age	0.002 ± 0.008	0.787
Sex	0.043 ± 0.166	0.797
MELD Score	0.020 ± 0.011	0.079
PPI Use	0.607 ± 0.179	< 0.001[b]
Model 3, other medications		
Age	0.004 ± 0.008	0.647
Sex	0.033 ± 0.164	0.839
MELD Score	0.024 ± 0.011	0.041[a]
Lactulose	0.324 ± 0.189	0.089
PPI use	0.625 ± 0.178	< 0.001[b]

[a]$P < 0.05$,
[b]$P < 0.01$. B ± SE: beta ± standard error. MELD: Model for end-stage liver disease; PPI: Proton pump inhibitor.

ARTICLE HIGHLIGHTS

Research background

Proton pump inhibitors (PPIs) are a recent hot topic in both internal medicine and gastroenterology, mostly because of their widespread use. Studies are quickly demonstrating that these medications may not come without risk, as recent studies have demonstrated a clear association between PPI and conditions like osteoporosis, pneumonia, *Clostridium difficile*, and some even postulate an association with dementia. While many effects of PPIs are still in question, it has also been shown that PPIs work by acid suppression, which can disrupt the gut microbiome. Patients with cirrhosis are at risk to develop hepatic encephalopathy (HE), primarily through ammonia produced by typical gut flora, and could subsequently be at risk for changes in this condition if the microbiome is altered in any way.

Research motivation

The main topic we are trying to address is whether PPI overuse can lead to additional effects aside from those previously mentioned and described in the literature. One particularly vulnerable population is those with cirrhosis, as ammonia production is affected by the gut microbiome. Solving this problem would allow future therapeutics to focus on the gut-liver-microbiome axis to prevent or lessen the severity of HE.

Research objectives

The main objective we want to demonstrate is the effect of PPI on the degree of HE. We hope to draw an association between PPIs and HE to encourage further prospective research studies on the side effects of PPIs, the gut microbiome in relation to HE, and to further aid in hospital outcomes for patients with cirrhosis.

Research methods

This is a retrospective analysis of patients with liver cirrhosis who were admitted with an ICD-9 and/or ICD-9 diagnosis of HE. Once these patients were identified, a chart analysis was performed to determine if these patients were on a PPI for > 30 d prior to their hospital admission. Those who were on a PPI for > 30 d were compared to patients who were not on a PPI at all in relation to their hospital stay. A linear regression model was applied to all patients to confirm the absence of any confounding variables.

Research results

During our analysis, we found that patients on a PPI who were admitted with HE subsequently had a significantly longer hospital stay, significantly worse grade of HE, and a larger percentage of those had intensive care unit (commonly known as ICU) admissions during their hospital stay. These findings suggest that patients should be assessed for the need for PPIs at every visit. This also points to the gap in knowledge between PPI and HE, especially if future research is able to demonstrate changes in the gut microbiome in patients on PPIs.

Research conclusions

In summary, in this retrospective medical chart review, PPI use was shown to be associated with worsened HE, greater length of hospital stays, and higher rate of ICU admissions in cirrhotic patients. To our knowledge, this is the first study that demonstrated that PPI use is associated with worse grades of HE, whereas prior studies by Tsai *et al* and Hung *et al* demonstrated higher risk of HE and overall higher mortality, respectively, in an Asian population. We propose that PPI use might affect cirrhotic patients by altering gastric pH, leading to the proliferation of gut micro-biome, thereby increasing ammonia production and bacterial translation. Considering the recent increased prevalence of PPIs, this study provides clinically relevant information regarding their potential risks in the cirrhotic population.

Research perspectives

As a retrospective review, our study is limited by incomplete data collection and uneven distribution of PPI user and non-user groups. However, the observation that PPI users experience worsen HE and longer hospital stays is clinically important. Future randomized-controlled studies will help confirm this observation and guide clinicians in a shift away from the use of PPI in cirrhotic patients.

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