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Stress Peptic Ulcers in a Sample of Iraqi Patients

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Abstract

Background Psychological stress may cause stress peptic ulcers, regardless of *Helicopecter pylori* (*H. pylori*) infection or use of non-steroidal anti-inflammatory drugs (NSAID). Studies of sociodemographic characteristics and peptic ulcers identified various risk factors, such as low salary, household member crowding, unemployment, marital strain, and psychological and physical stress.

Objective To determine the clinical picture of stress peptic ulcer in a sample of Iraqi patients.

Methods A cross-sectional study was performed in Al-Imamein Al-Khadimein Medical City, Iraq to determine the clinical features of stress peptic ulcer in a sample of Iraqi patients. Sample collection was done in a period of two years, from April 2021, to April 2023. At first, the process was explained to the patients and informed consent taken from all enrolled individuals. The diagnosis of stress peptic ulcer was done by gastroduodenoscopy, or by laparotomy for acute abdomen (perforated stress ulcer). All selected patients were tested for the presence of active *H. pylori* infection by stool antigen test (and it was negative). The patients were divided into two groups; Group A patients were presented as an (emergency cases) with complications of stress peptic ulcer either perforation or upper gastrointestinal bleeding stress ulcer; and Group B patients were presented with dyspepsia (as a cold cases), proved by gastroduodenoscopy to be due to stress peptic ulcer.

Results A total of 86 patients with stress ulcer, 37 (43.02%) males, and 49 (56.97%) females, their age ranged from 13-76 years (mean age 36.16±76 years). Group A were 31 (36.04%) patients, their presentations were either acute abdomen proved to be due to perforated stress ulcer by laparotomy in 8 (9.30%) patients, or hematemesis in 23 (26.74%) patients. Group B were 55 (63.59%) patients. The incidence of stress ulcer was 0.02% and the incidence of operations for perforated stress ulcer was 0.01%. The mortality rate was one (1.16%) old female patient with perforated stress ulcer.

Conclusion Stress ulcer can bleed and perforate, so there should be awareness about management of pain, stress and anxiety in all age groups. There should be good and effective postoperative analgesia, reassurance and empathy for patients and advice for protections against stress ulcer when needed.

Keywords Stress ulcer, bleeding, perforation

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List of abbreviations: DU = Duodenal ulcers, GIT = Gastrointestinal tract, *H. pylori* = *Helicopter pylori*, ICU = Intensive care unit, NSAID = none steroidal anti-inflammatory drugs, OGD = Oeophagogastroduodenoscopy, PTT = Partial thromboplastin time

Introduction

Understanding the etiology, investigation and treatment of peptic ulcer disease has changed markedly in recent years. Stress peptic ulceration commonly occurs in patients with major injury or illness, who have undergone major surgery or who have major comorbidity. Many such patients are found in intensive care units. There is no doubt that it is far better to prevent this condition than to try to treat it once it occurs. Endoscopic means of treating stress ulceration may be ineffective

and operation may be required. The principles of management are the same as for the chronic ulcer. Pain and psychological stress can cause peptic ulcers in patients with different age groups. Secondary peptic ulcer disease develops as a result of the acute stress of a severe systemic illness such as head trauma or overwhelming sepsis [1].

The prevalence of *Helicopecter pylori* (*H. pylori*) shows large geographical variations reaching up to 50% of the population in some developing countries [2].

The discovery of *H. pylori* switched the understanding of the etiology of peptic ulcer disease from that of an acid driven disease to an infectious disease [3]. Peptic ulcer disease has changed profoundly in the last decades in Western countries in both children and adults. Indeed, the prevalence of *H. pylori*-positive ulcers has declined, and a new disease has emerged: *H. pylori*-negative gastric or duodenal ulcers (DU) [4].

It is interested to ask whether ALEXANDER THE GREAT who died at age of 32 years, with acute abdominal pain may be due to stress peptic ulcer (the stress life of his great empire) [5]. Some of those patients with stress ulcer were presented with either dyspepsia, acute abdomen (proved to be due to perforated peptic ulcer), or with hematemesis due to severe pain (any sever pain whether it is renal colic or postoperative pain with inadequate analgesia). There are well known causes of peptic ulcer like *H. pylori* infection, non-steroid anti-inflammatory drugs (NSAID) and smoking, but still there are patients with peptic ulcer due to other causes [6]. It was mentioned in a study that 5-20% of patients with peptic ulcer are considered as idiopathic [7].

Researches and literatures advice more study about the pathogenesis of peptic ulcer disease [8]. It was mentioned in literatures that stress, depression and anxiety impair healing of peptic ulcer may be due to its effect on blood flow and gastric secretions [9]. A study on 233,093 Swedish males shows that decreased stress resilience significantly increased the risk of peptic ulcers [10].

Stress may promote peptic ulcer through increased acid load, effects of hypothalamic-pituitary-adrenal axis activation on healing, altered blood flow, or cytokine-mediated impairment of mucosal defenses. Some studies showed that behavioral mediators such as smoking, alcohol consumption and poor sleep may be behind the mechanism of stress peptic ulcer. Although one study showed that there is no synergy between stress and *H. pylori* and effect modification by socioeconomic status, other studies show the ability of stress to affect the course of *H. pylori* infection [11].

There are evidences to support the observations of the association between the effect of *H. pylori* infection on peptic ulcer development and socioeconomic status, age and tobacco smoking [12].

The observed 0.2% per-year rate of new ulcers during follow-up underestimates the true incidence rate, both because ulcers diagnosed as outpatients among subjects lost to follow-up were not included and because asymptomatic ulcers were unlikely to have been detected. Other studies not believe in stress as a cause of peptic ulcer [13]. Although some studies observe a decrease in the incidence of stress ulcer and its complications of bleeding and perforation in the United States as well as elsewhere, but still, it continues to cause substantial morbidity and mortality in the United States as well as elsewhere [14].

The aim of the study was to determine the clinical features of stress peptic ulcer and its complications in a sample of Iraqi patients.

Methods

A cross-sectional study was performed Al-Imamein Al-Khadimein Medical City, Baghdad, Iraq to determine the clinical features of stress peptic ulcer in a sample of Iraqi patients. Sample collection was done in a period of two years, from April 2021, to April 2023. At first, the process was explained to the patients and informed consent taken from all enrolled individuals. The study was approved by the

Institution Review Board in the College of Medicine Al-Nahrain University. The total number of patients attending the hospital in two years with acute abdomen was 621; operations done for 617 of them, and the other four patients were treated conservatively (their acute abdomen was due to non-surgical causes). The study population included 86 patients with stress peptic ulcer, aged 13–76-year-old who attended the hospital and were diagnosed to have stress peptic ulcer by endoscopic findings, or by laparotomy for acute abdomen (perforated stress ulcer). All selected patients were tested for the presence of active *H. pylori* infection by stool antigen test (and it was negative).

The patients were divided into two groups; Group A patients were presented as an (emergency cases) with complications of stress peptic ulcer either perforation or upper gastrointestinal bleeding stress ulcer; and Group B patients were presented with dyspepsia (as a cold cases), proved by gastroduodenoscopy to be due to stress peptic ulcer.

Group A patients were managed by resuscitation and emergency laparotomy for perforated peptic ulcer; while the patients with bleeding stress peptic ulcer were managed conservatively by resuscitation, gastroduodenoscopy and medical management. Group B patients were managed by conservative treatment for stress ulcer. All the patients had no risk factors of peptic ulcer other than stress (they were not smokers, negative biopsy for *H. pylori*, no take of NSAID, and no other risk factors of peptic ulcer other than stress).

The diagnosis was made with either patients attending the hospital with dyspepsia, perforated stress ulcer, or upper gastrointestinal tract (GIT) bleeding stress ulcer; or the patients were already admitted to the hospital and underwent operations for other diseases not related to the GIT, like nephrectomy for renal cell carcinoma, hernia operations, ureteric stricture and lower ureteric stone, and other diseases) and then they develop stress ulcer 1-2 postoperative day may be due to pain and inadequate postoperative analgesia, or psychological stress especially in patients with carcinoma.

Inclusion criteria

Patients presented with stress ulcer with no previous history of dyspepsia or peptic ulcer.

Exclusion criteria

1) Patients with history of dyspepsia or peptic ulcer.
2) Patients who had risk factors for peptic ulcer other than stress (like *H. pylori*, smokers, alcoholic, and NSAID or steroid users).

Statistical analysis

Analysis of data was done using the available statistical package of SPSS-27 (statistical packages for social sciences- version 27). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values) accordingly whether they were categorical or continuous.

Results

The total number of patients with stress ulcer was 86 patients, 37 males (43.02%), and 49 females (56.97%), their age ranged from 13-76 years, their mean age was 36.16±76 years. Their biopsies were negative for *H. pylori* and they had no history of other risk factors for peptic ulcer.

The incidence of stress ulcer during two years in this study was 0.02% of patients attending the hospital and the incidence of operations for perforated stress ulcer was 0.01%. The mortality was 1 (1.16%), and three (4.65%) patients need blood transfusion for upper GIT bleeding.

Group A (complicated stress ulcer; perforation and bleeding) were 31 (36.04%) patients; and Group B were 55 (63.59%) patients whom complain of dyspepsia (in the course of management for other diseases) and proved to be due to stress ulcer by gastroduodenoscopy and were treated accordingly.

In group A, there were 8 (9.30%) patients presented with acute abdomen proved to be

due to perforated stress ulcer by laparotomy, and 23 (26.74%) patients were presented with hematemesis proved to be due to stress ulcer by gastroduodenoscopy. Table 1 shows the distribution of study groups according to gender.

Table 1. Distribution of study groups according to gender

Group A (Complicated stress ulcer) (31)				Group B (Dyspepsia) (55)		Total
Bleeding stress ulcer (23)		Perforated stress ulcer (8)				
Male	Female	Male	Female	Male	Female	
7 (8.13%)	16 (18.60%)	4 (4.65%)	4 (4.65%)	26 (30.23%)	29 (33.72%)	86

In group A, 8 (9.304%) patients were developed perforated stress ulcer; 6(6.97%) patients of them were (out-patients) presented to the emergency department with acute abdomen proved to be due to perforated stress ulcer by laparotomy (they were unemployed poor patients with a lot of social and psychological problems and stress), while the other 2 (2.32%) patients were in-patients (they were admitted to the hospital and developed perforated peptic ulcer in the course of elective operations for other diseases). One of those in-patients 1 (1.16%) was a male with lower ureteric stricture and impacted lower ureteric stone and prepared for removal of the ureteric stone and implantation of the ureter, he was developed acute abdomen the night before the operation in the ward due to severe pain and inadequate analgesia for ureteric colic; laparotomy was done for him as an emergency condition (there was purulent peritonitis due to perforated peptic ulcer; cleaning of the peritoneal cavity and repair of the perforated stress ulcer with omental patch was done, then closure of the peritoneal cavity and removal of the lower ureteric stone with re-implantation of the ureter into the bladder), the patient improved and discharged well. The other in-patient 1 (1.16%) was an old female patient and developed acute abdomen in the second postoperative day (postoperative radical nephrectomy for renal cell carcinoma) and proved to be due to perforated stress ulcer by laparotomy but unfortunately the patient died second day due to fluid and electrolyte imbalance. So, the mortality rate was1 (1.16%) patient. Table 2 shows the distribution of patients presented with perforated stress ulcer in Group A.

Table 2. Distribution of patients presented with perforated stress ulcer in Group A

	Out-patients	In-patients		Total
Perforated stress ulcer	6 (6.97%)	Pre-operative (lower ureteric stricture and impacted lower ureteric stone)	1 (1.16%)	
		postoperative radical nephrectomy for renal cell carcinoma	1 (1.16%)	
Total	6 (6.97%)		2 (2.32%)	8 (9.304%)

In group A, there were 23 (26.74%) patients were presented with upper GIT bleeding, which proved to be due to stress ulcer by gastroduodenoscopy (with negative biopsy for *H. pylori* and there were no other risk factors for peptic ulcer like smoking, alcohol, or NSAID). There were 16 (18.60%) patients presented to the emergency room and out-patients with hematemesis due to stress (they were unemployed poor patients with a lot of social and psychological problems and stress). Three of them 3 (3.48%) were in-patients underwent operations for hernia repair and presented with hematemesis; two of them were young males developed hematemesis in the day of operation due to severe pain and inadequate analgesia, and the third patient was an old man who develops hematemesis during hernia repair under local anesthesia. Another three 3 (3.48%) patients were developed hematemesis proved to be due to stress ulcer by gastroduodenoscopy in the course of management of severe abdominal sepsis (in the course of operation not involving GIT). One female patient 1(1.16%) with mastectomy for breast carcinoma developed hematemesis proved to be due to stress ulcer by gastroduodenoscopy (due to severe pain, apprehension, and psychological stress due to cancer and loss her breast). Table 3 shows the distribution of patients presented with hematemesis due to stress ulcer in Group A.

Table 3. Distribution of patients presented with hematemesis due to stress ulcer in Group A

	Out-patients	In-patients		Total
Hematemesis	16 (18.6%)	Postoperative (hernia repair)	3 (3.48%)	
		Severe abdominal sepsis	3 (3.48%)	
		Postoperative (mastectomy)	1 (1.16%)	
Total	16 (18.6%)		7 (8.23%)	23 (26.74%)

Three (4.65%) patients with bleeding stress ulcer need blood transfusion. One (1.16%) old female patient who developed perforated stress ulcer second postoperative day after radical nephrectomy for renal cell carcinoma was developed peritonitis but unfortunately, she died second postoperative day (laparotomy for perforated peptic stress ulcer) due to sepsis and fluid and electrolyte disturbances. Table 4 shows the rate of blood transfusion and mortality in patients with complicated stress ulcer.

Table 4. Rate of blood transfusion and mortality in patients with complicated stress ulcer

Complicated stress ulcer	N (%)
Need for blood transfusion (patients with upper GIT bleeding)	3 (4.65)
Mortality (patients with perforated stress ulcer)	1 (1.16)

Discussion

Peptic ulcer disease has changed profoundly in the last decades in Western countries in both children and adults. Indeed, the prevalence of *H. pylori*-positive ulcers has declined, and a new disease has emerged: *H. pylori*-negative gastric or DU [4]. *H. pylori*-negative ulcers, due to unknown causes, are more frequent in

younger children, do not have a gender preference, and tend to have a higher recurrence rate, particularly in Chinese children [15]. In the past two decades, primary peptic ulcer disease has been more widely recognized as a diagnosis worthy of consideration in the pediatric age group. In the present study, a child presented with perforated stress ulcer; she was a 13 years old female child who was presented with acute right lower abdominal pain for one-day duration. On examination, there was tenderness and rebound tenderness in the right iliac fossa. She was considered as a case of acute appendicitis, and explored through a right grid iron incision; but surprisingly there was a fluid coming from upper abdomen through the right paracolic gutter, and so a second incision was made (upper midline incision) and the findings was a perforated stress ulcer in the first part of the duodenum anteriorly with generalized peritonitis. Cleaning of the peritoneal cavity and wash with normal saline and repair of the perforated duodenal ulcer with omental patch using vicryl sutures and anti-ulcer treatment was given. Her biopsy was negative for *H. pylori.* The patient had stress about her examination in her school. Peptic ulcers in children can be classified into primary and secondary ulcers. Secondary peptic ulcer disease develops as a result of the acute stress of a severe systemic illness such as head trauma or overwhelming sepsis. Excluding those secondary peptic ulcers, primary peptic ulcers are even less commonly seen in pediatric practice [16]. In Goggin, Ireland, founded that the age range was 9.8-14.25 years and that was near to the results of the current study [17]. Single-center series from different parts of the world showed that primary peptic ulcer disease was diagnosed in only 1.8-3.6% of the total number of upper endoscopies performed to investigate GIT symptoms in children [18]. *H. pylori* infection is considered to be the most important cause of primary DU in children, and eradication of the bacteria is effective in preventing ulcer relapse [19].

The second patient in this study was a 32 years old male patient who was admitted to the hospital as a case of impacted lower ureteric stone and ureteric stricture proved by contrast study (intravenous urography) with recurrent attacks of ureteric colic and was prepared for surgery next morning. At midnight suddenly he develops another type of sudden severe generalized abdominal pain, tenderness and rigidity. Exploration shows generalized peritonitis due to big perforated stress ulcer in the first part of the duodenum with generalized peritonitis. Surgical treatment of perforated stress peptic ulcer was done. Then closure of the peritoneal layer, exposure of the ureter, removal of the stone and surgical repair of the ureteric stricture was done (to treat and get rid of the main cause of his disease and primary pathology). Post-operative anti- peptic ulcer was given and the patient was improved. The cause of stress ulcer was severe recurrent attacks of pain due to ureteric colic with inadequate analgesia.

The third patient was 75 years old female patient underwent left radical nephrectomy for right renal cell carcinoma through a left paramedian incision. The patient was developed sudden sever generalized abdominal pain with generalized abdominal tenderness and rigidity in the first postoperative day. After resuscitation she was explored by laparotomy and a generalized peritonitis was found due to big perforated stress ulcer in the first part of the duodenum. Surgical treatment of perforated stress peptic ulcer was done. But unfortunately, the patient was died second postoperative day due to fluid and electrolyte imbalance and septicemia. Her stress ulcer was due to postoperative pain and stress.

The fourth patient was a 56 years old man was presented with sudden generalized abdominal pain with generalized tenderness and rigidity. Exploration showed generalized peritonitis due to perforated stress ulcer in the first part of the duodenum (the stress was due to socioeconomic state and poverty because he was unemployed). Surgical treatment of perforated stress peptic ulcer was done. The patient was improved and discharged well. The Fifth patient was a 20 years old young old

man was undergoing repair of inguinal hernia at morning and he was ready for discharge next morning, but he developed sudden attack of fresh bloody vomiting (hematemesis) proved to be due to stress peptic ulcer by gastroduodenoscopy next morning. After resuscitation and antiulcer treatment, the patient was discharged well.

The Sixth patient was a 72 years old man with obstructed inguinal hernia and unfit for general or spinal anesthesia and the surgical repair of his hernia was done under local anesthesia, he developed hematemesis during surgical repair of the hernia due to pain and stress. After resuscitation and proper management gastroduodenoscopy prove the presence of stress ulcer (the biopsy was negative for *H. pylori*) and there was no history of other causes and risk factors of peptic ulcer.

The seventh patient was a 37 years old poor man who had was unemployed and had a lot of social and economic problems presented with acute abdomen, which proved to be due to perforated big stress ulcer about one centimeter in diameter, he was develop postoperative leak from the site of repair of the ulcer for few days and pelvic abscess which was drained and treated accordingly then he improved and discharged well.

Many other patients were developed postoperative hematemesis proved to be due to stress ulcer by gastroduodenoscopy (their surgeries were not related to gastrointestinal canal, but their operations were mastectomy for breast carcinoma, and different types of hernias (without opening the bowel).

So, after those patients, there was a lot of concern about the condition with good and enough postoperative analgesia and reassurances with early alarm for any dyspepsia. Many patients whom complain of (even mild dyspepsia) were underwent gastroduodenoscopy, a lot of them had stress ulcer proved by gastroduodenoscopy, and was treated appropriately without complications of neither bleeding nor perforation.

Literatures and scientific researches prove the effect of stress in creation of peptic ulcer and its complications. Levenstein et al. concluded that psychological stress increased the incidence of peptic ulcers, regardless of H. pylori infection or NSAID use [6].

Other literatures found that participants with the highest self-perceived stress level had a 2.2-fold higher risk of peptic ulcer treatment in 33 months of follow-up compared to participants with the lowest level of stress. The cumulated incidence of treatment was approximately 1.2% for those with the highest stress levels and 0.4% for those with the lowest levels of stress [20,21].

In a sample of 233,093 Swedish males, decreased stress resilience significantly increased the risk of peptic ulcers [13]. Melinder et al. found that low stress resilience in adolescent males increased the risk of peptic ulcers in adulthood compared with high stress resilience [10]. Ruigómez et al. reported increased odds of peptic ulcers in a nested case control study among patients who had been diagnosed with stress before their peptic ulcer diagnosis [8], and Levenstein et al. found an increased risk in another Danish sample using a stress index preceding 12 years of follow-up [6].

Other studies found that stress should be considered a determinant of peptic ulcer disease. Numerous studies of sociodemographic characteristics and peptic ulcers identified various risk factors, such as low salary, household member crowding, unemployment, marital strain, psychological and physical stress, and previous peptic ulcers. These findings were supported by several previous studies. Anda et al. found an increased risk of peptic ulcers in individuals with self-perceived stress during the month preceding baseline. The study further found evidence of a graded relationship between levels of self-perceived stress and the risk of a peptic ulcer [22]. Wachirawat et al. also found evidence of higher increased odds of a peptic ulcer in patients with high self-perceived stress levels [23]. Some studies found that there are association between *H. pylori* infection and stress. Stress affected *H. pylori*-related ulcers at least as much as those related to neither non-steroidal anti-inflammatory drugs nor *H. pylori*. These results support a multicausal model of

peptic ulcer etiology with intertwined biological and psychosocial components. Clinicians treating ulcer patients should investigate potential psychological stress among other risk factors. Rosenstock et al. found that individuals in a Danish sample with *H. pylori* infection had a significantly lower odds ratio for reporting mental stress than those with no infection [(14)]. On the other hand, some studies show that not all the patients with *H. pylori* or NSAID drug developed ulcers, and in 16-31% of ulcers neither can be implicated so there are other factors must be implicated [(24)] and still the role of psychological stress considered as one of the risk factors for peptic ulcer and should be taken into account [(25, 26)]. Examining life stress at baseline among a defined Danish population cohort in relation to medically confirmed ulcers during the next 11-12 years; had suggested associations with psychological factors and there is a complementary effect of psychological, social, behavioral, and bacteriologic factors in development of stress ulcer.

A vast literature links peptic ulcer to stress and many other researchers showed that ulcer diagnoses after societal stressors such as wartime bombing or earthquake [(27-29)] and worsening of prognosis by psychological factors [(30-32)].

Other cross-sectional studies were unconvincing, because the results were inaccurate due to the distressing effects of disease [(33)]. Previously histamine-2 blockers, and proton pump inhibitors were available only by prescription and patients with dyspepsia were investigated for peptic ulcer using oeseophagogastrodeuodenoscopy (OGD), so, the incidence of ulcer was accurately evaluated, but nowadays dyspepsia is commonly self-treated [(34)], so, many ulcers remain undiagnosed [(35)]. The incidence of uncomplicated ulcer was decreased and although the incidence of complicated stress ulcer (bleeding and perforation) is also decreased, but they carry high morbidity and mortality in the United States and worldwide. The stress index used had the merit of taking into account objective life stressors such as unemployment as well as the subjective distress. A high perceived stress-level was associated with an increased risk of peptic ulcers. The group with the highest stress level had a 2.2-fold increased risk of having a peptic ulcer compared to the individuals with the lowest stress level. Cohen's perceived stress scale has been validated as a measure of stress with consistent results for decades [(36)]. There is a suggestion to give stress ulcer prophylaxis therapy when indicated; if the patient has one of the following four major risk factors: (coagulopathy {platelet count of 1.5, partial thromboplastin time (PTT) of >2 times the control}; mechanical ventilation longer than 24 hours; recent GIT ulcers/bleeding within 12 months of admission; traumatic brain injury, traumatic spinal cord injury, or thermal injury {>35 percent of the body surface area}. Stress ulcer prophylaxis therapy also given if the patient has two or more of the following minor risk factors: (sepsis, shock, intensive care u nit (ICU) >1-week, occult bleeding within 6 days, high dose corticosteroids {250 mg hydrocortisone, 50 mg methylprednisone}, hepatic failure, renal failure, organ transplantation, administration of non-steroidal anti-inflammatory agent, or injury severity score >15). The use of intragastric enteral nutrition may have additive cytoprotective effects when used in conjunction with histamine 2 receptor blockers, but whether administration of intragastric enteral nutrition alone provides adequate protection is controversial. Patients with stress-related mucosal damage have much higher mortality rates than those without (57% vs. 24%) that's why the advice for stress ulcer prophylaxis therapy [(37)].

In conclusion, stress ulcer can bleed and perforate, so there should be awareness about management of pain, stress and anxiety in all age groups. There should be good and effective postoperative analgesia, reassurance and empathy for patients and advice for protections against stress ulcer when needed.

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Conflict of interest
The author declares that have no conflict of interest.

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