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# Hyperglycemia-related risk factors in enteral nutrition in non-critically ill patients

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**Abstract**
*Introduction:* Carbohydrate metabolism can change in hospitalized patients due to stress, or the use of enteral nutrition (EN). The aim of this study was to determine the risk factors triggering these changes.
*Material and Methods:* We conducted a retrospective observational study in non-diabetic patients with low levels of stress on EN. Five groups were categorized based on changes to the metabolism of hydrocarbons produced before or after EN: plasma glycemia prior to EN >126 mg/dL (stress hyperglycemia – SH) (35.1%); plasma glycaemia prior to EN <126 mg/dL (non-HE) (64.89%). Hyperglycemia with EN (HyperEN): at least, two capillary blood glucose readings >140 mg/dL or 1 >180 mg/dL during EN (71%); non-HyperEN: capillary blood glucose readings with EN <140 mg/dL (29%).
*Results:* A total of 131 patients were included (45.8% men) with a median age of 81 (71–87) years. A total of 52 patients exceeded 180 mg/dL at one measurement, and 24 patients required insulin detemir with a median of 16 (12–27) IU per day. Risk factors for HyperEN were identified as patient age (OR, 1.186; 95% CI, 1.051–1.341; $p < 0.01$) and duration of nutritional treatment (OR, 1.320; 95% CI, 1.086–1.605; $p < 0.01$).
*Conclusions:* Our study shows a high prevalence of carbohydrate metabolism disorders in hospitalized patients on total EN, with age and duration of nutritional treatment being the main risk factors.


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Hiperglucemia asociada a nutrición enteral;
Diabetes

**Factores de riesgo relacionados con la hiperglucemia en nutrición enteral en pacientes no críticos**

**Resumen**
*Introducción:* El metabolismo de los carbohidratos puede verse alterado en pacientes hospitalizados debido al estrés (HE) o al uso de nutrición enteral (NE). El objetivo de este estudio fue determinar los factores de riesgo que favorecen estas alteraciones.
*Material y métodos:* Estudio observacional retrospectivo en pacientes no diabéticos con bajo estrés en tratamiento con NE completa. Se diferenciaron cinco grupos según las alteraciones en el metabolismo hidrocarbonado producidas antes o después de la NE: glucemia plasmática antes de la NE >126 mg/dl (HE) (35,1%); glucemia plasmática antes de NE <126 mg/dl (NoHE) (64,89%). Hiperglucemia con NE (HiperNE): al menos dos lecturas de glucemia capilar superiores a 140 mg/dl o una superior a 180 mg/dl durante la NE (71%); No HiperNE: lecturas de glucemia capilar con NE inferiores a 140 mg/dl (20%).
*Resultados:* Se incluyeron 131 pacientes (45,8% varones) con una mediana de edad de 81 (71-87) años. 52 pacientes excedieron los 180 mg/dl en una determinación. 24 pacientes requirieron insulina detemir con una mediana de 16 (12-27) UI/día. Los factores de riesgo para HiperNE se identificaron como la edad del paciente (OR=1,186 IC95% 1,051-1,341; p<0,01); y la duración del soporte nu tricional (OR=1,320 IC95% 1,086-1,605; p<0,01).
*Conclusiones:* Nuestro estudio muestra una alta prevalencia de trastornos del metabolismo hidrocarbonado en pacientes hospitalizados con nutrición enteral completa, siendo la edad y la duración del soporte nutricional los principales factores de riesgo.


## Introduction

Disease-related malnutrition (DRM) can affect different population groups, with hospitalized patients being one of the most affected ones.[1] Poor nutritional status favors comorbidities, increases the risk of complications or even mortality in hospitalized subjects.

Nutritional screening tools allow us to identify these patients and assess those who require nutritional treatment,[2] which is indicated in patients with malnutrition or who are unable to meet their oral requirements for a long period of time. Enteral nutrition (EN) is the nutrition of choice when the functionality of the GI tract is maintained. It is a safe and effective technique, with complication rates from 16% up to 70% depending on the definition used and the population studied.[3]

Hospitalized patients may have elevated blood glucose levels without a previous history of diabetes mellitus (DM). This is known as stress hyperglycemia (SH). Prevalence ranges from 4% up to 12% and is associated with increased morbidity and mortality rates.[4,5] Some treatments, such as EN, can lead to hyperglycemia. This alteration has been more studied in patients on parenteral nutrition, however, there are few studies in the case EN. Although the prevalence of hyperglycemia in enteral nutrition (HyperEN) is unknown, it is through to affect between 30% and 47% of the patients and in half of the cases there is no previous diagnosis of diabetes (DM).[6] Hyperglycemia in EN is associated with more complications and with the length of stay.[7]

Clinical practice guidelines and expert consensus recommend monitoring of blood glucose levels and set targets of pre-prandial blood glucose levels <140 mg/dL and at any other time <180 mg/dL for hospitalized patients, both targets in and out of the critical care unit.[8] These targets can be changed based on the patient's clinical situation, associated comorbidities and age to achieve acceptable control and reduce the risk of complications, such as hypoglycemia.[9]

Insulin is the most effective treatment to achieve these goals. A small number of studies have assessed the safety and effectiveness of different insulin administration regimens in these patients.[10,11] Subcutaneous regimens are primarily used in patients on EN. However, the use of insulins has many risks such as increased hypoglycemia.[12] On the other hand, the knowledge of the factors that may favour the development of hyperglycemia in EN will allow early intervention or prevention of hyperglycemia.

Specific nutrition formulas adapted for diabetes have been developed to improve glycemic control and reduce insulin requirements. These are preparations with a lower carbohydrate amount, a high amount of fermentable fibre and an increased percentage of predominantly monounsaturated fats that do not worsen the lipid profile. The use of these formulas is often limited to patients with knowing diabetes mellitus or SH.[13] Nevertheless, some patients could have a high risk of hyperglycemia, which the use of these formulas could prevent. For this reason, it is important to know the risk factors to developing hyperglycemia in patients on EN.

There are not many studies evaluating risk factors of hyperglycemia in patients on EN, although it is a very common complication in patients on EN that can affect both diabetic and non-diabetic patients. The aim of this study

was to analyze which factors may be associated with hyperglycemia in EN in non-diabetic patients with low levels of stress and an indication for EN.

## Material and methods

### Study design

We conducted a retrospective observational study of 131 hospitalized non-diabetic patients with low levels of stress. EN with normocaloric-normoprotein formula was started within 48 h of admission. Patients were recruited from January 2014 through December 2019.

The study was evaluated and approved by Hospital Clínico Universitario de Valladolid (HCUVA) Ethics Committee with code PI 20-1915. This study was conducted in full compliance with the clinical practice guidelines established in the Declaration of Helsinki.

### Study population

The study population was non-diabetic patients admitted to the hospital who were unable to meet their energy requirements orally.

The inclusion criteria were (1) non-diabetic patients admitted to the hospital, (2) patients with low levels of stress (patients not admitted to critical care units), (3) indication for total EN, and (4) collection of capillary blood glucose during EN for, at least, 2 days.

Exclusion criteria: (1) patients younger than 18 years, (2) patients from the ICU/coronary care unit, (3) patients who have started EN at the ICU/coronary care unit setting, (4) pregnant patients, (5) patients diagnosed with diabetes mellitus or with glycated hemoglobin (HbA1c) levels >6.5% at admission, and (6) patients with allergies or intolerance to any of the components from the EN formula.

## Study variables

### Patient characteristics

The parameters recorded were age, sex, reason for admission, and duration of admission.

The Charlson Index was used to assess the 10-year survival based on the comorbidities recorded in the patients' clinical history. Calculation was performed using the following tool http://www.samiuc.es/indice-de-comorbilidad-de-charlson-cci/.[14]

### Nutritional assessment and enteral nutrition

The nutritional status was determined using laboratory parameters, such as albumin at admission. The diagnosis of malnutrition was established using the Global Leadership Initiative on Malnutrition (GLIM) criteria and the subjective global assessment test (SGA).

The GLIM criteria required, at least, one phenotypic and one etiologic criterion for the diagnosis of malnutrition. Patients were categorized into two groups: (A) well-nourished and (B) malnourished.[15]

In the SGA test, variables from the health history, physical examination and biochemistry were collected. Patients were categorized into two groups: (A) well-nourished; (B and C) at risk of malnutrition.[16]

Energy expenditure was calculated using the estimated formula of 25–30 kcal × kg of body weight.[17]

The C-reactive protein (CRP) was measured prior to starting EN (Roche Diagnostics autoanalyzer) as an indicator of the patients' levels of stress.

The duration of EN from the initiation of EN until the patient recovered the oral route or was discharged was collected.

### Carbohydrate metabolism parameters and study groups

Blood plasma HbA1c and glucose (chemiluminescence immunoassay using a Roche Diagnostics autoanalyzer [Basel, Switzerland]) were analyzed before starting EN. Capillary blood glucose tests (Free Style Optium Neo® Glucometer) were performed every 8 h during the EN period.

Capillary blood glucose targets were set as pre-prandial values <140 mg/dL and at any other time <180 mg/dL for hospitalized patients. Hypoglycemia was defined as capillary blood glucose values <70 mg/dL.

Patients were categorized into three study groups:

- *Stress hyperglycemia (SH)*: patients with plasma glycemia before starting EN >126 mg/dL.
- *Non-stress hyperglycemia (non-SH)*: patients without have plasma glycaemia before starting EN >126 mg/dL. In these patients non-SH was categorized into two groups: EN-related hyperglycemia (HyperEN): patients with, at least, 2 capillary blood glucose levels >140 mg/dL or 1 >180 mg/dL during EN. Non-EN-related hyperglycemia (NoHyperEN): patients with capillary blood glucose levels during EN <140 mg/dL.

The nutrition unit monitored capillary glycemia and insulin treatment was prescribed based on hospital protocol. This protocol included: a sliding scale with Lispro insulin according to capillary glycemia (values >150 mg/dL); all patients with capillary glycemia >150 mg/dL were started on basal insulin (detemir) at a calculated dose of 0.2 IU/kg bw/day divided into two doses (9:00 AM and 9:00 PM). Treatment with insulin was initiated in patients with SH and EN-related hyperglycemia.

The mean dose of insulin detemir required by patients and the time on EN until starting with the insulin was collected.

### Statistical analysis

Qualitative variables were expressed as absolute and relative frequencies (percentages) and quantitative variables as mean and standard deviation (SD) in the case of normal distribution or as median and interquartile range (p25–p75) if distribution was non-normal. To study the association between qualitative variables, the chi-square test was used, with Yates correction and Fisher's exact test when needed. In the case of quantitative variables,

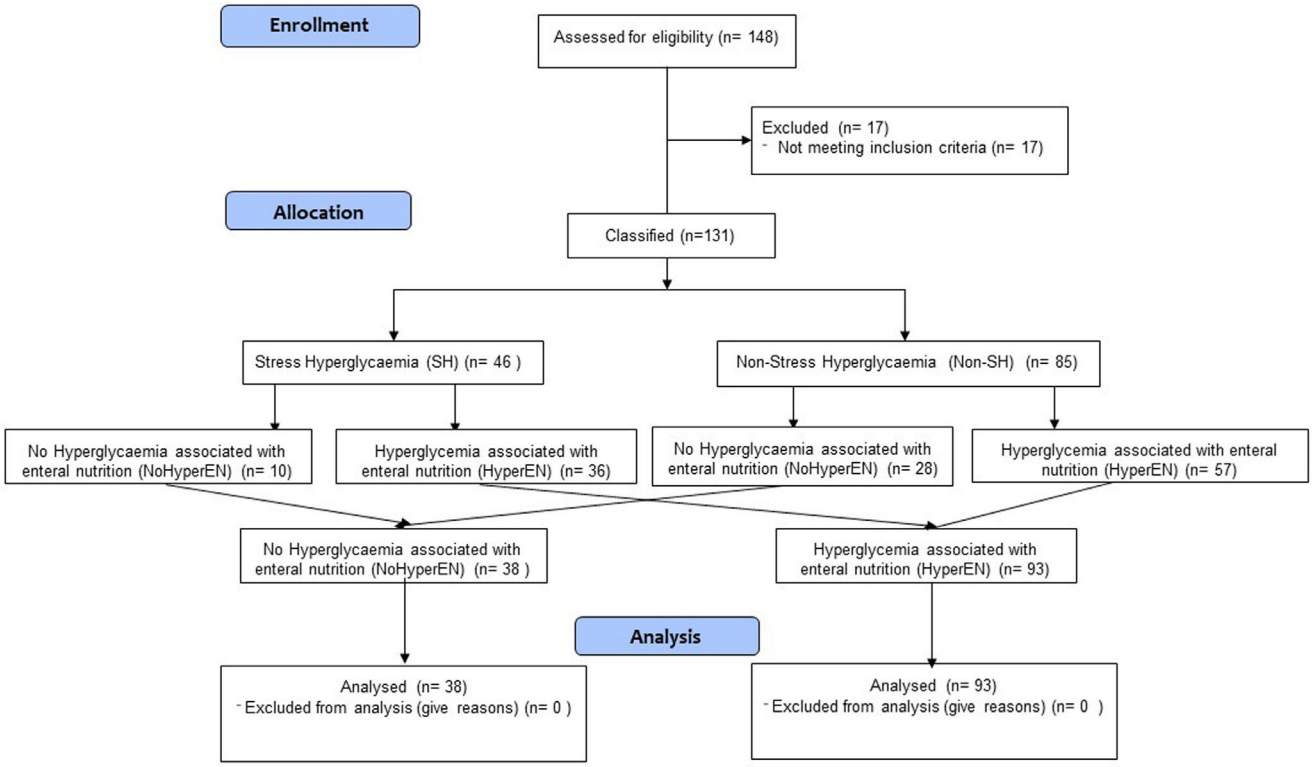


**Figure 1** Flowchart.

the Kolmogorov–Smirnov test was used to determine the normality of the distributions. To study differences across independent means, the parametric or non-parametric statistical tests required by the application conditions were used (Student's *t*-test or Mann–Whitney *U* test). The sample was stratified according to variables that could act as confounding factors. The main study objective was analysed using multivariate regression. Statistical significance was considered for a *p*-value of less than 0.05. SPSS software was used (SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA, 2006)).

## Results

### Patient characteristics

The median age of the sample was 81 (71–87) years; 60 (45.8%) were men. The mean Charlson Index score was 4 (3–5) points. The mean length of stay was 12 (8–17) days.

The main reason for admission was cerebrovascular disease (81.7%), followed by respiratory conditions (6.9%).

A total of 48.27% of the patients were malnourished or at risk of malnutrition according to SGA and 78% according to GLIM. Nutritional requirements were estimated at 25–30 kcal/day, but a mean of 22.0 (5.19) kcal/day was achieved, with a mean duration of EN of 7 (4–10) days.

Flowchart of the study is shown in Fig. 1.

### Characteristics of carbohydrate metabolism

A total of 17 patients were excluded because they had HbA1c levels >6.5% at diagnosis.

Of note, 108 patients had, at least, blood glucose levels with EN >140 mg/dL while 52 patients >180 mg/dL in one measurement. A total of 6 patients had hypoglycemia.

A total of 46 patients (35.1%) developed SH. Comparing the No SH and SH group variables, differences were only observed in mean capillary blood glucose during EN 129 (115–143) vs 141 (126.13–157.13) mg/dL $p < 0.01$ and in final dose of insulin levemir 13 (10.5–16) vs 23 (17–31.50) units $p < 0.01$. No difference was observed in the duration of admission 11 (7–16.5) vs 13 (9–23.5) days $p = 0.06$. Of the SH group, 36 patients (29%) had subsequent hyperglycemia in EN.

Ninety-three patients (70.9%) had EN-related hyperglycemia (HyperEN). The differences in the different variables according to the cohort analysed (NoHiperEN–HiperEN) are shown in Table 1.

Seventy one patients (54.2%) received subcutaneous rapid rescue insulin and 24 patients (18.3%) required insulin detemir. Median initiation of insulin detemir was 4 (2–6.75) days from the start of EN and a median dose of 16 (12–27) units. Four episodes of hypoglycemia were observed with no differences detected between the HyperSH and non-HyperSH groups.

In the adjusted multivariate analysis, patient age and days on EN remained as risk factors for the development of hyperglycemia in EN (Table 2).

## Discussion

Hyperglycemia is a common complication in the EN patient regardless of the history of diabetes mellitus. This study demonstrates that the duration of nutritional treatment and

**Table 1** Comparison of variables in patients with NoHiperEN and HyperEN.

| | NoHyperEN 38 (29%) | HyperEN 93 (70.9%) | *p*-Value |
|---|---|---|---|
| Age (years) | 74 [55.25–84.25] | 83 [73.5–88.00] | <0.01 |
| Sex (male) | 20 (52.6%) | 40 (43%) | 0.32 |
| Length of stay (days) | 8.5 [5–14] | 13 [9–18.5] | <0.01 |
| Charlson Index | 3 [1–4] | 4 [3–5] | <0.01 |
| Malnutrition (SGA) | 11 (28.95%) | 40 (43.01%) | 0.12 |
| Malnutrition (GLIM) | 22 (58.89%) | 56 (60.21%) | 0.93 |
| Albumin (g/dL) | 3.73 ± 0.326 | 3.56 ± 0.52 | <0.01 |
| C-reactive protein (mg/dL) | 16.95 [8.93–48.55] | 39.5 [19.70–74.33] | <0.01 |
| kcal/kg | 20.32 ± 7.05 | 22.70 ± 4.05 | 0.06 |
| Duration of enteral nutrition (days) | 5 [2–8.25] | 7 [4–11.5] | <0.01 |

**Table 2** Adjusted multivariate analysis remained as risk factors for the development of hyperglycaemia in enteral nutrition.

| | *B* | Odds ratio | 95% CI | | *p*-Value |
|---|---|---|---|---|---|
| | | | Inferior | Superior | |
| Age | −1.71 | 1.186 | 1.051 | 1.341 | 0.006 |
| Sex (male) | 0.278 | 1.321 | 0.346 | 5.043 | 0.684 |
| Charlson Index | −0.751 | 0.472 | 0.190 | 1.172 | 0.106 |
| Albumin | −0.038 | 0.963 | 0.207 | 4.476 | 0.962 |
| C-reactive protein | 0.014 | 1.015 | 0.998 | 1.031 | 0.077 |
| kcal/kilo | 0.092 | 1.096 | 0.954 | 1.259 | 0.195 |
| Duration of enteral nutrition | 0.278 | 1.320 | 1.086 | 1.605 | 0.005 |

the age of the patient are risk factors for the development of associated hyperglycemia during EN.

Our study presents a very elderly population with prolonged lengths of stay, which is similar to another study conducted in the same region, in which the mean length of stay was more than 15 days.[18] The main reason for admission was stroke. Cardiovascular disease, along with neurological disease are the main reasons for hospital admission.[19] For the assessment of comorbidities, we used a widely used index in literature (the Charlson Index)[20] whose main objective is to predict the severity of patients regardless of the main diagnosis.

In our study, malnutrition was assessed using the subjective global assessment. A total of 49% of the population was malnourished according to the SGA test. This rate is higher vs other studies such as that of Martineau et al., a study of 73, 19.2% of whom were malnourished. This difference is possible because we included patients at risk of malnutrition in the assessment.[21] A total of 78% of patients were malnourished according to GLIM criteria. In the study by Nozoe et al., 28.7% were malnourished. This difference may be due to the fact that they were young patients with a median age of 72 years vs 81 years in our study.[22] However, in a study of 188 patients whose age was more similar to that of our population (78.9 ± 7.7 years), malnutrition according to GLIM criteria was 64.8%,[23] similar to that of our study.

EN attempts to adjust the patient's nutritional requirements based on nutritional needs. In our case, estimated equations were used for the calculation. Caloric intake should be adjusted to avoid providing more calories than required, as this can lead to poor glycemic control. In our study, caloric intake was somewhat lower than the recommended guidelines of 25–30 kcal/day.[17]

Despite being a non-diabetic population, at the follow-up, a total of 108 patients had capillary blood glucose levels >140 mg/dL and 52 > 180 mg/dL. This is a major complication vs other studies where estimates for hospitalized patients are somewhere between 32% and 38%. According to these results, capillary blood glucose monitoring should be performed in hospitalized patients regardless of their previous metabolic status because of its relationship with the development of complications and because it is a good opportunity to identify unknown diabetic patients.[10,24]

One third of the sample had SH probably related to the acute situation and 71% of the sample had EN-related hyperglycemia. In our study, most patients were admitted with cerebrovascular disease. These patients are more likely to have metabolic stress-related hyperglycemia. In the systematic review by Capes et al., the rates of hyperglycemia on admission of stroke patients stood somewhere between 8% and 63% according to the investigator's diagnostic criteria. In our case, the rate of hyperglycemia was 35%, so the prevalence in our study was within this range.[25]

Among the epidemiological variables, no differences are observed between patients with SH and those without it. Former studies, such as those by Umpierrez[26] or Russo[27] prove the existence of these expected differences during admission, which may be due to the fact that the sample size of our study probably cannot detect the significant difference in this variable.

González-Infantino et al.[6] observed that in-hospital hyperglycemia triggered worse outcomes in patients requiring EN. Our data show that the monitoring of mean capillary blood glucose during enteral treatment and the presence of severe hyperglycemia were more common in the SH group. There were also differences in the percentage of patients requiring insulin detemir and in the final dose, so SH may worsen the patients' glycemic status.

In our study, patients with EN-related hyperglycemia were older. Also, the work of González-Infantino et al. confirmed that there was a greater likelihood of developing hyperglycemia in those who were older.[6] There are differences in albumin and CRP values prior to starting EN, probably due to a more catabolic situation due to the stressful situation of the group that developed hyperglycemia during enteral treatment.

In our population, the same nutrition formula was used in all patients, an isocaloric normoprotein formula. Patients who developed hyperglycemia on EN were given a higher caloric load ($22.70 \pm 4.05$ kcal/day vs $20.32 \pm 7.05$ kcal/day) vs those without this complication. These data are similar to those by other studies, such as that of Hasanloei et al. in a critical population.[28]

In our study, the prevalence of hypoglycemia was low, only 4.5% of the sample had an episode of hypoglycemia (values <70 mg/dL). No differences were reported between the group that developed hyperglycemia while on EN and the group that did not, in those patients who received subcutaneous insulin therapy.

Given the high prevalence of changes in carbohydrate metabolism in this study, we aimed to study the factors that may impact the rise of blood glucose levels during EN. The predictors of hyperglycemia obtained after multivariate analysis were the age of the patients and the days on EN, which can lead us to prevent this type of hyperglycemia with the use of diabetes specific formulas in patients at risk. A recent study by López-Gómez et al. proved that the use of a high protein normocaloric formula reduces the development of EN-related hyperglycemia.[29]

Patients who developed hyperglycemia during nutrition were on EN longer than those who did not develop. These data are consistent with those by González-Infantino reported in 1004 patients. This has been attributed to the fact that these patients have a more torpid evolution or are more complicated, requiring greater hospital treatment and slower recovery from the oral route.[6] Insulin resistance also predominates in the regulation of carbohydrate metabolism in hospitalized patients. This alteration is more or a problem in the older population because the mechanisms of homeostasis are more severely impaired.[30] It is therefore consistent that age and the duration of nutritional treatment is a risk factor for the appearance of this complication.

The strengths of this study are mainly that it was conducted in the real clinical practice and was, therefore, easily generalizable to hospitalized patients, conducted exclusively in non-diabetic patients and that standardized biochemical determinations, such as glycated hemoglobin and capillary plasma glycemia were used to classify the changes in carbohydrate metabolism.

The main limitation of our study is its retrospective design with the possible loss of data. Another limitation is its heterogeneity and sample size that may limit extrapolating results to other populations.

## Conclusions

In the present study, the prevalence of carbohydrate metabolism changes was found to be very high in non-critically ill patients without a past medical history of diabetes on EN. A total of 35.6% developed SH and 71% hyperglycemia while on EN. The most important risk factors for the development of hyperglycemia while on EN were age and duration of nutritional treatment. The presence of these two factors should help us identify patients at risk and monitor them more closely with the possibility of early intervention if necessary.

It would be interesting to design prospective studies to compare the impact of on carbohydrate metabolism on enteral formulas adapted for diabetes in the non-diabetic population, as well as the different treatment regimens for glycemic control.

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None declared.

## Conflict of interest

The authors declare that they have no conflict of interest.

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