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RESEARCH ARTICLE

The effects of LactoCare synbiotic administration on chemotherapy-induced nausea, vomiting, diarrhea, and constipation in children with ALL: A double-blind randomized clinical trial

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Abstract

Background: Synbiotics are supplements containing probiotics and prebiotics and potentially have a stronger effect in modulating the gut microbiota than probiotics or prebiotics alone. The aim of this study was to determine the effects of LactoCare synbiotic administration on chemotherapy-induced diarrhea (CID), nausea, vomiting, and constipation in children with acute lymphoblastic leukemia (ALL) who receiving maintenance chemotherapy.

Methods: This double-blind clinical trial was performed on 113 children with ALL. The patients were randomly assigned into two groups to receive either 5×10^9 CFU LactoCare synbiotic administration or placebo (58 patients in the LactoCare-treatment group and 55 patients in the placebo group), twice a day for 7 days. The number of times CID, vomiting, nausea, and constipation were recorded in the first week after the beginning of receiving LactoCare and the placebo.

Results: In the LactoCare-treatment group, CID was present in 3.7% and 1.8% of patients on the first and second days, respectively, and no CID was observed on the third to seventh days ($p < .05$). While in the placebo group, the rate of patients with CID on the second, third, and fourth days was 11.5%, 13.5%, and 11.5%, respectively, and less than 10% on the first, fifth, sixth, and seventh days. It was observed that the rate of constipation in the LactoCare-treatment group was significantly lower than in the placebo group. The difference between the groups was about 14% on the third day, which increased to about 20% on the sixth day ($p < .05$).

Conclusion: The use of synbiotic supplements in this study reduced CID in patients. This study supports the concept that the use of synbiotic supplements will be an easy and effective way to reduce CID in ALL patients.

KEYWORDS
chemotherapy, constipation, diarrhea, LactoCare, nausea, vomiting

Abbreviations: ALL, acute lymphoblastic leukemia; CID, chemotherapy-induced diarrhea; CINV, chemotherapy-induced nausea and vomiting; CI, confidence interval; ECOG, European Cooperative Oncology Group; ITT, intent-to-treat; OR, odds ratios; SD, standard of deviation.

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1 | INTRODUCTION

The most common adverse reactions to chemotherapy are chemotherapy-induced nausea and vomiting (CINV), mucositis, neutropenia, constipation, and chemotherapy-induced diarrhea (CID).[1–3] They can lead to anorexia, weakening of the psychological and social status of patients weight loss, nutritional deficiencies, electrolyte imbalance, and dehydration.[4] The severity of CINV and CID depends on the individual patient risk factors and the emetogenic risk of the prescribed chemotherapy agents.[5] Patients with untreated CINV and CID often need additional office visits, prolonged hospitalization, and even emergency department visits.[6] In addition, the occurrence of CINV and CID can alter or interrupt subsequent chemotherapy cycles and affect the optimal treatment of malignancy, resulting in delayed complete remission and survival of patients.[7,8] Therefore, CINV and CID undoubtedly affect the quality of life of patients.

Chemotherapy can cause painful ulcerative lesions in the mouth, which act as a site of secondary infection.[9] The microenvironment of the intestinal microbiota contains a large number of bacteria, which in this way plays a key role in maintaining intestinal homeostasis, metabolism, nutrition, and defense against pathogens.[10,11] Chemotherapy can cause disorders of the gastrointestinal tract through changes in the intestinal microbiota and disrupting the colonization of intestinal bacteria. This event caused the growth of pathogenic bacteria, which is associated with side effects, such as diarrhea, vomiting, and constipation.[12,13]

Probiotics are live, nonpathogenic bacteria that improve the activity of intestinal flora and alter the intestinal microbial flora through replacement or colonization, thus having a beneficial effect on the host's health.[14,15] In addition, the role of probiotics in improving homeostasis and reducing side effects related to anticancer treatments has been shown in previous studies.[16,17]

Synbiotics refer to supplements that contain both probiotics and prebiotics in a form of synergy and potentially have a stronger effect in modulating the gut microbiota than probiotics or prebiotics alone.[18] The aim of this study was to determine the effects of LactoCare synbiotic administration (as a supportive treatment) on diarrhea, nausea, vomiting, and constipation in children with acute lymphoblastic leukemia (ALL) who receiving maintenance chemotherapy.

2 | METHODS AND MATERIALS

2.1 | Ethics consideration

Ethical principles were followed based on the ethical protocol approved by the Ethics Committee at Arak University of Medical Sciences, Arak, Iran (IR.ARAKMU.REC.1396.166) and the Declaration of Helsinki. The trial was registered at the Iranian Registry of Clinical Trials as IRCT20150119020715N5. In order to obtain the consent form, the objectives of the study were first explained to the parents, and then the consent form was obtained from the children's parents.

TABLE 1 The contents of the active LactoCare capsules.

Lactobacillus casei
Lactobacillus acidophilus
Lactobacillus rhamnosus
Lactobacillus bulgaricus
Bifidobacterium breve
Bifidobacterium longum
Streptococcus thermophilus
Prebiotic fructooligosaccharides

2.2 | Study subjects

This double-blind, randomized (allocation ratio 1:1) and pilot study were conducted over 12 months from May 2020 through May 2021. All children with ALL admitted to the pediatric ward were included in the study. All children aged 5–15 years with a diagnosis of ALL receiving maintenance chemotherapy.

The sample size was calculated based on a study power of 80% with type one error (α) of 5% and confidence level of 95% using SPSS 25.0 software (Inc., Chicago, IL, USA). A total of 121 patients with ALL were randomized in this study for eligibility, considering 20% dropouts in each group.

Randomization was done using a computerized random number table and based on the simple randomization method by a biostatistician inside the clinic. In this way, the patients were randomly divided into a synbiotic-treatment group and a placebo group.

2.3 | Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the patients aged 5–15 years, (2) patients who were able to swallow the medicine, (3) no history of treatment with radiotherapy 6 months before the study, (4) no antipsychotic disease, and (5) had a European Cooperative Oncology Group (ECOG) performance status ≤ 2.

Exclusion criteria: (1) patients who had an active infection, digestive tract tumors, cardiac arrhythmia, gastrointestinal disorders, primary central nervous system disorders, bowel obstruction, cardiovascular disorders, and liver and kidney disorders within the previous 6 months; (2) patients with Covid-19 and uncontrolled diabetic mellitus; (3) patients with hypersensitivity, respiratory problems, hypertension, and severe infection; (4) patients with nausea, vomiting, and diarrhea 1 week before the study; (5) patients who had a history of taking antibiotics in the last 15 days; and (6) patients with neutropenia and fever.

2.4 | Study intervention

Patients with ALL were included in the study and treatment with probiotics started on the day of the first dose of chemotherapy.

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	Definition	Count the number of times
Diarrhea	Feces as puree or liquid, very fast transit	
Nausea	A sick feeling in the child's stomach, especially when it was accompanied by an aversion to food and an involuntary urge to vomit, Or When the child said that "he/She wants to vomit"	
Vomiting	The act of emptying the contents of the stomach through the mouth spasmodically	
Constipation	Hard stools, slow transit	
Number of supplements taken per day:		

FIGURE 1 Diarrhea, nausea, vomiting, and constipation recording form.

In the LactoCare-treatment group, patients received 5×10^9 CFU of LactoCare (prepared by Zisttakhmir Company, Iran), by mouth, twice a day for 7 days. LactoCare capsules contain seven bacterial strains mentioned in previous studies (Table 1).[19] LactoCare was refrigerated at 4°C before use in patients. In the placebo group, patients received placebo (prepared by Zisttakhmir Company, Iran), by mouth, twice daily for 7 days. The placebo capsules (starch) were prepared in the shape and size of the original drug by the same company. LactoCare and placebo were labeled by nurses A and B, respectively, so that both study investigators and patients were blinded to treatment allocation during the study as well as outcome measurement. Then, by assigned an identification code to the patients, this nurse proceeded to distribute the labeled therapeutic products among the patients according to a randomization schedule. Outcomes were measured based on labeled therapeutic products and patient identification codes.

Parents of hospitalized children were asked not to stop taking the drug arbitrarily during the study. In addition, a daily reminder message was sent to parents' mobile phones to use supplements. In order to determine the level of adherence to treatment, parents were asked to write down the number of supplements taken in the questionnaire form in Figure 1. In addition, counting the containers of therapeutic agents was also used to determine the level of adherence to treatment. The rescue medication used for CINV and CID was metoclopramide and loperamide, respectively. The rescue medications were used when CINV and CID occurred more than three times per day.

2.5 | Evaluation of CID and CINV

CID and CINV were recorded in the first week after the beginning of receiving LactoCare and the placebo. The patient's parents were asked to write down the number of times diarrhea, vomiting, nausea, and constipation after chemotherapy in the notebook according to the guidance sheet that was given to them (Figure 1). Data were recorded daily. During the study, a coordinator was in contact with the patient's parents to ensure the correctness of the recorded information. The characteristics of the evacuations were assessed according to the Bristol scale.

2.6 | Statistical analysis

Statistical analyses were performed using SPSS 25.0 software (Inc., Chicago, IL, USA) and a genetic analyzer (ABI PRISM 310, Applied Biosystems). The mean and standard deviation (Mean ± SD), Pearson's χ^2 test (or Fisher's exact test), and Student t-test were used to compare the two groups' characteristics. Univariate analysis was performed to investigate the risk factors of diarrhea, constipation, nausea, and vomiting, and then multivariate logistic regression analysis was performed if a significance level of less than 10% was observed in univariate analysis. $p < .05$ was considered a statistical difference.

3 | RESULTS

A total of 113 patients (54 patients in the LactoCare-treatment group and 52 patients in the placebo group) completed the study, as presented in the CONSORT diagram (Figure 2). Medical records were available for all patients. Included patients' ages ranged from 5 to 15 years. The mean age of patients in the LactoCare-treatment group and placebo group were 8.15 ± 2.13 and 8.54 ± 2.41, respectively. In total, 59 patients were male and 47 were female. The demographic characteristics of both study groups are summarized in Table 2. Baseline characteristics were similar in both groups with regard to gender, age, and ECOG ($p > .05$).

One week after the administration of LactoCare, the total number of gastrointestinal complications including diarrhea, constipation, vomiting, and nausea in the LactoCare-treatment group compared to the placebo group was 2.3 versus 6.2 events per patient, which was divided by the total number of complications by the total number patients in each group were calculated. In other words, the complications observed in the LactoCare-treatment group were significantly lower than the placebo group ($p < .05$). Moreover, the rate of nausea,

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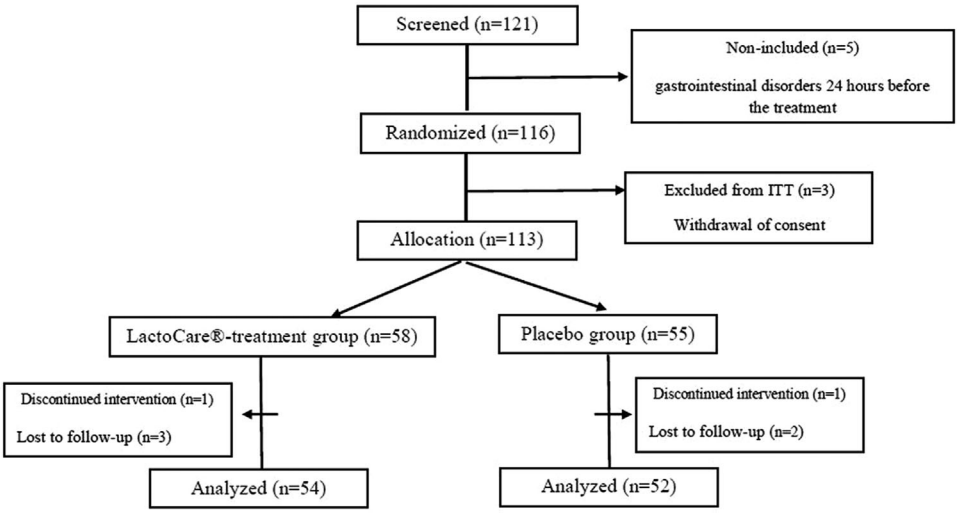

FIGURE 2 Flowchart of study procedure. ITT; intent-to-treat population.

TABLE 2 Patient characteristics.

Characteristics	LactoCare-treatment group ($N = 54$)	Placebo group ($N = 52$)	*p*-Value
Gender, *n* (%)			
Male	32 (59.3)	27 (52.0)	.558[a]
Female	22 (40.7)	25 (48.0)	
Age, years ± SD	8.15 ± 2.13	8.54 ± 2.41	.330[b]
Mean weight ± SD (kg)	29.1 ± 12.6	30.3 ± 11.2	.421[b]
Mean body mass index ± SD (kg/m^2)	15.3 ± 2.2	15.5 ± 1.7	.891[b]
ECOG[c] performance status			
0–1	38 (70.4)	35 (67.3)	.835[a]
2	16 (29.6)	17 (32.7)	

Note: Data are No. (%) unless otherwise indicated.
Abbreviations: SD; Standard of deviation, *n*; number.
[a]Pearson's χ^2 test was used.
[b]Student *t*-test was used.
[c]ECOG; Eastern Cooperative Oncology Group.

vomiting, diarrhea, and constipation was analyzed separately (Figure 3). In the LactoCare-treatment group, diarrhea was present in 3.7% and 1.8% of patients on the first and second days, respectively, and no diarrhea was observed on the third to seventh days ($p < .05$). While in the placebo group, the rate of patients with diarrhea on the second, third, and fourth days was 11.5%, 13.5%, and 11.5%, respectively, and less than 10% on the first, fifth, sixth, and seventh days. None of the patients in the LactoCare-treatment group used rescue treatment, whereas 7.7% of the patients in the placebo group needed to use this treatment.

It was observed that the rate of constipation in the LactoCare-treatment group was significantly lower than in the placebo group. The difference between the groups was about 14% on the third day, which increased to about 20% on the sixth day ($p < .05$). In addition, from the second day onward, constipation was observed in a greater proportion in the placebo group, until on the seventh day, about 17% difference between the two groups was observed ($p < .05$).

The incidence of nausea and vomiting was lower in the LactoCare-treatment group with a difference of more than 10% on the seventh day of the effects of LactoCare synbiotic administration ($p < .05$).

The odds ratios and 95% confidence interval were calculated to evaluate the use of LactoCare as a protective factor against nausea, vomiting, diarrhea, and constipation (Table 3). The placebo group in our study was 1.45 times more likely to have diarrhea compared to the LactoCare-treatment group ($p = .048$, odds ratio: 1.45; confidence interval: 1.17–4.01).

4 | DISCUSSION

The use of synbiotics supplementation in children with ALL as a target group has been specifically considered in the present study. In this study, the reduction of some gastrointestinal side effects caused by chemotherapy was shown after the administration of synbiotics and considering this issue, we suggest them as a useful supportive agent to reduce diarrhea, vomiting, nausea, and constipation. As the parents were encouraged to take the drugs every day, there was no interruption, and the children tolerated the taste. The results also demonstrate that patients who received LactoCare in our study were 1.45 times less likely to have diarrhea compared to those who received placebo ($p = .048$, odds ratio: 1.45; confidence interval: 1.17–4.01).

The importance of using synbiotics in reducing gastrointestinal complications has also been shown in previous studies.[20] Consistent with our results and with an odds ratio like ours, Hassan et al. in their study found that the use of probiotics is a protective factor for diarrhea and

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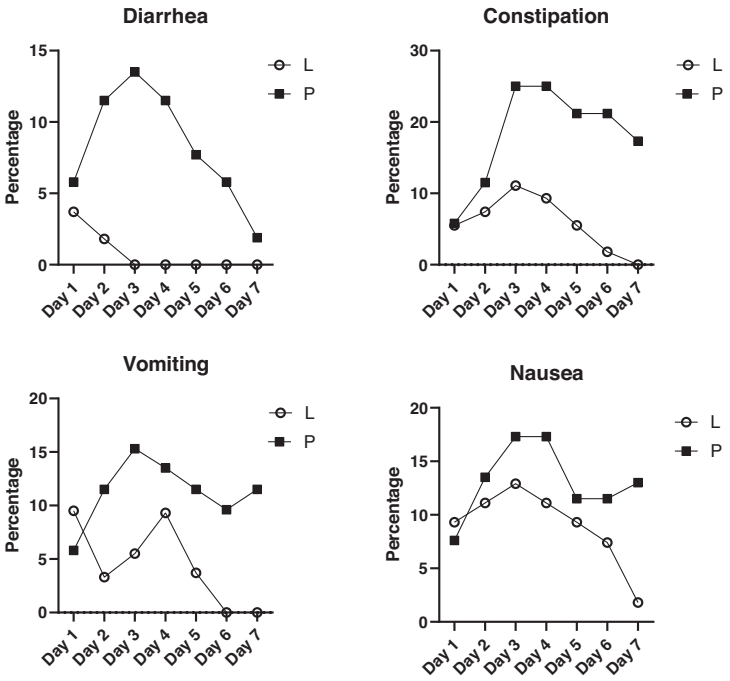

FIGURE 3 Percentage of patients with diarrhea, constipation, vomiting, and nausea per day according to the study group.

TABLE 3 Modeling odds of diarrhea, constipation, vomiting, and nausea caused by chemotherapy in two groups.

Treatment group: Placebo vs. LactoCare	OR[a] (95% CI)	*p*-Value	OR[b] (95% CI)	*p*-Value
Diarrhea	2.51 (1.35–4.13)	.015	1.45 (1.17–4.01)	.048
Constipation	1.51 (0.52–5.64)	.310	0.98 (0.27–2.12)	.617
Vomiting	1.26 (0.61–1.45)	.298	1.31 (0.27–1.74)	.534
Nausea	1.22 (0.34–3.65)	.561	1.36 (0.37–4.26)	.219

Abbreviations: 95% CI, confidence interval; OR, odds ratios.
[a]Univariate analysis.
[b]Multivariate analysis.

may reduce incidence of septicaemia.[21] In another systematic review and meta-analysis, Wang et al. evaluated the efficacy and safety of probiotics for prevention of CID in patients with abdominal and pelvic cancer. The authors found that supplement of probiotics could reduce the incidence of CID induced by radiotherapy. Moreover, their results revealed that there may be a rare risk of probiotics-associated infection, sepsis, and bacteremia.[22] However, meta-analysis studies have shown that current studies are not enough to evaluate the successful effectiveness of probiotics in patients with cancer and more studies are needed in this field.[23]

Probiotics have a beneficial effect in reducing the symptoms of chronic intestinal disease in adults and improving the disease. Few studies have been conducted on the administration of probiotics in children with cancer. However, a reduction of gastrointestinal symptoms in children with acute diarrhea after the administration of probiotics has been reported.[24,25] Gastrointestinal side effects that are observed in many patients with cancer after chemotherapy affect the quality of life of patients to the extent that they can delay or stop treatment.[20,26] Gastrointestinal side effects have been reported in 40%–100% of patients with cancer, depending on the standard or high chemotherapy dose.[2] For example, it has been reported that about 50% of patients with cancer still have diarrhea and constipation after chemotherapy, whose episodes may continue up to 10 years after stopping treatment.[27]

The use of probiotics to treat or prevent diarrhea has been evaluated in some studies, but their results are somewhat contradictory due to the difference in the type of cancer examined in the patients and also the formulation of probiotics.[28,29] In the current study, the rate of diarrhea in the LactoCare-treatment group was significantly lower than the placebo group, so in the LactoCare-treatment group, diarrhea was recorded in a small percentage of patients only in the first 2 days, while in the placebo group, diarrhea was recorded in all the days of the study and in a higher percentage of patients were recorded. Considering that rescue treatment was not used for CID patients, it is concluded that the use of synbiotics can be associated with a reduction in the use of rescue treatment. Consistent with our results, a recent study on the incidence of diarrhea in children with acute leukemia reported that none of the patients receiving probiotics experienced diarrhea from

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the first day to the end of the study.[20] Similar results were reported in another study that evaluated the effect of a probiotic containing live *Lactobacillus acidophilus* LA-5 plus *Bifidobacterium animalis* subsp. *lactis* BB-12 to prevent radiation-induced diarrhea in cervical patients with cancer.[29] However, other studies, inconsistent with our study, have reported that the use of probiotics does not reduce gastrointestinal complications, including diarrhea.[30,31] Among the reasons for the difference in the results of different studies, we can mention the content of probiotics/synbiotics used and the type of cancer studied, as well as different treatments, including high-dose or standard chemotherapy and radiotherapy.

The role of probiotics as a potential new therapeutic tool in modulating microbiota-gut-brain interactions has been demonstrated in rats; however, there are no human studies on constipation.[32,33] Reports on the improvement of constipation after using probiotics are different and although improvement has been observed with some strains, no evidence of improvement has been observed with other strains.[33] In this study, a significant difference was observed in the prevalence of constipation in the two groups, so there was a difference of more than 15% from the third day of consumption onward. This result is repeated in the study by Reyna-Figueroa et al., wherein they assessed probiotics in the prevention of chemotherapy-induced gastrointestinal side effects in patients under 17 years of age diagnosed with acute leukemia.[20] There is evidence that shows the effect of probiotics in reducing gastrointestinal complications, including constipation, maybe through modulating the mucosal immune barrier or the systemic immune barrier and improving the sensory and motor function of the intestine.[34] Therefore, depending on their content, probiotics/synbiotics may have a beneficial effect on constipation by influencing gut microbiota and fermentation.

There are conflicting results regarding the use of probiotics in immune compromised patients. Some studies have shown that the administration of probiotics in immunosuppressed patients increases the risk of infectious complications.[35,36] In other studies, the authors reported that *Lactobacillus rhamnosus* can be used as a first-line treatment to relieve diarrhea in premature infants and immunosuppressed patients, including those undergoing radiotherapy.[37,38] Moreover, in a meta-analysis study, the authors analyzed 57 clinical studies and presented that the administration of probiotics and/or synbiotics in immunocompromised adults is safe according to the evaluated probiotic strains, doses, and duration. There were also no major safety concerns in these studies, as none of the serious adverse events were related to the probiotic or synbiotic product, and the products were well tolerated. They concluded that overall, adverse events occurred less frequently in immunocompromised subjects receiving probiotics and/or synbiotics compared to controls.[39]

There have not been many studies on the use of synbiotics to prevent nausea and vomiting. A pilot study done in 60 acute leukemia patients under 17 years of age by Reyna-Figueroa et al. used probiotic capsules containing *L. rhamnosus* GG with a concentration of 5×10^9 CFU per sachet. In that study, the difference between probiotic and placebo groups was 20% on the fourth day, which increased up to 40% on the seventh day. In addition, vomiting was found in a lower proportion in the probiotic group, with a difference between groups of 26% on the seventh day.[20] In the current study, the incidence of CINV was lower in the LactoCare-treatment group with a difference of more than 10% on the seventh day of synbiotics administration. One of the possible mechanisms of action of synbiotics may be due to the correction of dysbiosis, although the exact mechanisms still need further investigation. Therefore, it could be hypothesized by three potential mechanisms in the correction of dysbiosis: (1) reducing intestinal pH by lactobacilli and preventing the growth and reproduction of pathogens; (2) reducing the severity of intestinal inflammation through the regulation of immunomodulation; (3) stimulating the production of lactase and thus reducing damage to the intestinal villi.

One of the limitations of this study was that culture and microbiology analysis was not done on the stool samples of the studied patients in order to find and compare the concentration of pathogenic bacteria in the two groups.

In conclusion, the use of synbiotics supplement in this study reduced CID in ALL patients. This study supports the concept that the use of synbiotics supplement will be an easy and effective way to reduce CID in ALL patients. Studies related to changes in the dosage of synbiotics used and also the use of other strains to make synbiotics are suggested. Considering that digestive tract disorders can be seen even up to 3 weeks after chemotherapy in other types of cancer, it is also suggested to conduct more studies in other types of cancer with a longer period of time after chemotherapy.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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