Autologous Serum Therapy in Chronic Idiopathic Urticaria

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ABSTRACT

BACKGROUND

Chronic Urticaria (CU) is a common and distressing dermatosis and its treatment is challenging to the clinician. Autologous Serum Skin Test (ASST) is the simplest screening method to identify the immune response in chronic idiopathic urticaria. Autologous Serum Therapy (AST) is a modified form of autohemotherapy found to be effective in chronic idiopathic urticaria. We wanted to evaluate the effectiveness of autologous serum therapy in both ASST positive and ASST negative patients with chronic idiopathic urticaria.

METHODS

This study included 110 patients diagnosed to have chronic idiopathic urticaria who attended Dermatology outpatient department, Government Medical College, Kottayam, Kerala, from October 2016 to September 2017. Detailed history was taken and clinical examination was done along with relevant investigations in all cases. ASST was done, and patients were categorized into ASST positive and negative patients. All patients were given AST weekly once for a continuous period of 9 weeks and were followed up for 3 months. Total Severity Score (TSS) were recorded and the response was categorized into significant, moderate, and poor response, based on 6 parameters which were number of wheals, size of wheals, intensity of pruritus, duration of wheals, frequency of appearance of symptoms and frequency of antihistamine use.

RESULTS

Majority of patients were in the fourth decade with a female preponderance. Out of 110 patients, 32 were ASST positive and 78 were ASST negative. In ASST positive patients, thyroid antibodies were found in 46.9% and 10.3% in ASST negative patients. 6 parameters of TSS score were gradually reduced in both groups till the end of follow up period. Better and earlier response of TSS score to AST was noted in ASST positive patients. The difference in response to AST between ASST positive and negative groups was not statistically significant. Out of 32 ASST positive patients 20 (62.5%) showed significant response whereas out of 78 ASST negative patients 32 (41%) showed significant response. Only 4 (12.5%) out of 32 ASST positive patients showed poor response compared to 25 (22.7%) in ASST negative patients.

CONCLUSIONS

Autologous serum therapy is a safe and effective mode of treatment in the management of chronic idiopathic urticaria. ASST positive as well as negative patients showed response to AST but it tends to be more effective and earlier in ASST positive patients.

KEYWORDS

Chronic Idiopathic Urticaria, Autologous Serum Skin Test, Total Severity Score, Autologous Serum Therapy

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DOI: 10.18410/jebmh/2020/307

How to Cite This Article:
Valapil AP, Issac CM, Vineetha M. Autologous serum therapy in chronic idiopathic urticaria. J. Evid. Based Med. Healthc. 2020; 7(30),1453-1458. DOI: 10.18410/jebmh/2020/307

Submission 15-05-2020,
Peer Review 20-05-2020,
Acceptance 23-06-2020,
Published 27-07-2020.

BACKGROUND

Urticaria is defined as a skin lesion consisting of localized intracutaneous oedema (wheal) which is surrounded by an area of redness (erythema) that is typically pruritic.[1] Urticaria can be classified by both time course of symptoms and the underlying aetiology. Acute urticaria is defined as having skin-symptom duration of less than 6 weeks.[2] Chronic Urticaria (CU) is a common and distressing dermatosis characterised by the appearance of evanescent wheals almost daily, continuously for six or more weeks. The aetiology of chronic urticaria could be associated with conditions such as hormonal disturbances, autoimmune diseases, physical triggers, infections and idiopathic.[3] chronic idiopathic urticaria (CIU) is manifested as widespread wheals, where a predominant physical cause has been excluded.[4] chronic idiopathic urticaria encompasses 2 subgroups. One subgroup is of auto immune chronic urticaria due to auto antibodies against either high affinity IgE receptor FcεRI or less commonly IgE, whereas second subgroup of which comes about 30-50% remain truly idiopathic.[5]

Autologous Serum Skin Test (ASST) is the simplest screening method to identify the immune response in chronic idiopathic urticaria. Intradermal injection of autologous serum in immune patients elicits an immediate type wheal and flare response.[6] Autologous Serum Therapy (AST) is a modified form of autohemotherapy which has been found to be fairly effective in cases of chronic idiopathic urticaria.[7] The effectiveness of AST has been proved beyond doubt in ASST positive patients and a few studies from northern parts of India also claimed its effectiveness in ASST negative patients also.[4]

There were only a limited number of studies from southern parts of India especially Kerala that evaluates the effectiveness of AST. This study evaluate the effectiveness of AST which would be given to both ASST positive as well as ASST negative patients with chronic idiopathic urticaria for nine consecutive weeks starting one week after ASST with a follow up period of twelve weeks after completion of the treatment.

METHODS

This study was done in department of D & V, Government medical college Kottayam, Kerala and it was an open labelled prospective study for a period of 12 months from October 2016 to September 2017. After obtaining institutional review board approval, 110 patients with a clinical diagnosis of chronic Idiopathic urticaria were taken. Informed consent was obtained from all patients. Patients less than 12 years age, physical and all known exogenous causes of urticaria and infections, pregnant women, patients on immunosuppressive drugs were excluded from the study. Detailed history were taken including age, sex, occupation, time of onset, duration of symptoms, number of episodes per week, duration of lesions, angioedema, associated symptoms like nausea, vomiting, diarrhoea, abdominal pain, dizziness, syncope, dyspnoea, palpitations etc. Symptoms of other systemic illness like fever, cough, headache, jaundice, joint pains were noted.

Detailed food history, drug history, application of topical agents including cosmetics and medications were taken in detail. Questions were asked with specific attention to physical factors which trigger the wheals like exposure to heat, cold, water, sunlight, pressure and sweating. History of atopy, acid peptic disease and also detailed past and family history of the patients were noted. History of co-existing skin or other systemic diseases especially thyroid, autoimmune and endocrine disease were noted.

Detailed clinical examination including general and systemic examination including pulse rate, blood pressure, respiratory and gastro intestinal system were done. Detailed examination were carried out to find any focus of underlying infections. Routine blood, urine, stool examination and blood sugar estimation were done in all cases. Thyroid function tests, Anti thyroglobulin antibody, Anti TPO antibody, HBsAg, HCV and HIV 1 and 2 screening were done in patients included in the study. Also patients were asked to stop antihistamines 2 days prior to the onset of therapy.

Autologous Serum Skin Test- 2 mL of patient's blood was taken in a sterile test tube and centrifuged at 2000 rpm for 10 minutes. The test was performed by injecting 0.05 mL of patient's own serum intradermally into the flexor aspect of left forearm and a saline control 2 inches away. Reading of the wheal was taken after 30 minutes. A wheal and flare of more than 1.5 mm at serum site compared to the control site was considered positive.

Autologous Serum Therapy- 5 mL of venous blood of the patients was taken with a sterile, disposable syringe from antecubital vein in a sterile test tube. Blood was subjected to centrifugation at the rate of 2000 rpm for 10 minutes at room temperature. 2 mL of fresh serum separated from patient's blood was given deep IM into gluteal region for 9 consecutive weeks starting one week after ASST.

Urticaria Total Severity Score and Follow up Visits- Patients were continuously monitored based on total severity score (TSS) during the 9 consecutive weeks of treatment starting one week after ASST followed by 12 weeks of follow up visits with a total of 3 follow up visits (1 visit per month).

Parameter Scores	0	1	2	3
Number of wheals	None	≤20	21-50	>50
Size of wheals	None	<2cm	2-3cm	>3cm
Intensity of pruritis	None	Mild	Moderate	Severe
Duration of wheals	None	<1hr	1-12hrs	>12 hrs
Frequency of appearance	None	≤Once a week	2-3 times	Daily
Frequency of antihistamines	None	≤Once a week	2-3 times	Daily
Total Severity Score				

Criteria for Assessing Response

Urticaria Total Severity Score (TSS) quantifies the disease activity depending on the wheal number and size.[5] TSS calculated from number and size of wheals, intensity of pruritus, duration of persistence of lesions, frequency of appearance of lesions and frequency of antihistamine use,

with each parameter having a score of 0-3, maximum score being 18.[5] Patients response was measured as significant (if up to 75% decrease in score from the baseline), moderate (up to 50% decrease in score from the baseline),poor response (<50% decrease in the score from the baseline). The data was entered in Microsoft excel and further statistical analysis was done using SPSS software.

RESULTS

The age of the patients with chronic urticaria ranged from 13-63 years with the mean age being 36.17. The maximum number of patients were 29 in the age group of 31-40 years. Out of 110 cases 72 were females & 38 were males with female to male ratio 1.9:1. Among the 110 patients evaluated 32 patients (29.1%) were found to be ASST positive and 78 (70.9%) were ASST negative.

Age Distribution among ASST Positive and Negative Patients

The mean age of ASST positive group was 35.03 ± 13.44 (ranges from 15-63). The mean age of ASST negative group was 36.64 ± 12.48 (ranges from 13-62). There was no significant difference in the mean age between the groups. Among the 32 ASST positive patients, 20 were females (62.5%) and 12 were males (37.5%). Among the 78 ASST negative patients, 48 were females (61.5%) and 30 were males (38.5%).

Associated Comorbidities in ASST Positive Patients

In ASST positive patients, thyroid antibodies were found to be positive in 46.9%. Diabetes mellitus and atopy were found in 21.9% each. Among ASST negative patient's most common coexisting condition was found to be atopy (20.5%) Diabetes mellitus was present in 15.4% of cases. Thyroid antibodies were noted in 10.3%. TSS calculated from number and size of wheals, intensity of pruritus, and duration of persistence of lesions, frequency of appearance of lesions and frequency of antihistamine use. Each parameter in ASST positive and negative patients are compared. Baseline value of number of wheal score in ASST positive patients, is 2 ± 0.000 (mean ± S.D.) and in ASST negative patients, 2 ± 0.00. At 21st week the value is 0.56 ± 0.71 in ASST positive patients and 0.81 ± 0.77 in ASST negative patients (Table -1) The response of ASST positive group was earlier than that of negative group and the difference became significant in the sixth week (p value 0.028).

The baseline value for size of wheal score in both ASST positive and negative groups were comparable. The response of ASST positive group was earlier than that of negative group and the difference was significant in the sixth week (p value 0.035). (Table-2).

No. of Wheals	ASST Positive (n=32) Mean ± S.D.	ASST Negative (n=78) Mean ± S.D.	P Value (between Groups)
Baseline	2 ± 0.00	2 ± 0.00	0.00
1st week	1.97 ± 0.17	1.99 ± 0.11	0.195
2nd week	1.97 ± 0.17	1.97 ± 0.15	0.746
3rd week	1.94 ± 0.24	1.92 ± 0.31	0.626
4th week	1.91 ± 0.29	1.83 ± 0.49	0.099
5th week	1.69 ± 0.47	1.69 ± 0.69	0.378
6th week	1.50 ± 0.50	1.54 ± 0.78	0.028
7th week	1.34 ± 0.54	1.37 ± 0.83	0.00
8th week	1.16 ± 0.62	1.14 ± 0.87	0.00
9th week	0.81 ± 0.69	0.86 ± 0.81	0.087
13th week	0.66 ± 0.70	0.83 ± 0.79	0.390
17th week	0.59 ± 0.71	0.82 ± 0.78	0.591
21st week	0.56 ± 0.71	0.81 ± 0.77	0.702

Table 1. Comparison of Number of Wheal Score in ASST Positive and ASST Negative Patients Receiving AST

Size of Wheals	ASST Positive (n=32) Mean ± S.D.	ASST Negative (n=78) Mean ± S.D.	P Value (between Groups)
Baseline	2.78 ± 0.42	2.77 ± 0.42	0.785
1st week	2.69 ± 0.53	2.63 ± 0.51	0.541
2nd week	2.44 ± 0.56	2.35 ± 0.55	0.587
3rd week	2.06 ± 0.51	2.13 ± 0.56	0.377
4th week	1.91 ± 0.45	1.94 ± 0.61	0.727
5th week	1.72 ± 0.52	1.74 ± 0.74	0.451
6th week	1.53 ± 0.50	1.59 ± 0.82	0.035
7TH week	1.38 ± 0.55	1.41 ± 0.88	0.00
8th week	1.19 ± 0.59	1.15 ± 0.89	0.00
9th week	0.81 ± 0.69	0.86 ± 0.82	0.071
13th week	0.63 ± 0.70	0.85 ± 0.80	0.386
17th week	0.59 ± 0.71	0.85 ± 0.80	0.428
21st week	0.56 ± 0.71	0.85 ± 0.80	0.443

Table 2. Comparison of Size of Wheal Score in ASST Positive and ASST Negative Patients Receiving AST

Intensity of Pruritis	ASST Positive (n=32) Mean ± S.D.	ASST Negative (n=78) Mean ± S.D.	P Value (between Groups)
Baseline	2.88 ± 0.33	2.76 ± 0.43	0.003
1st week	2.56 ± 0.56	2.54 ± 0.52	0.735
2nd week	2.25 ± 0.56	2.14 ± 0.50	0.069
3rd week	1.94 ± 0.56	1.99 ± 0.52	0.655
4th week	1.72 ± 0.56	1.79 ± 0.86	0.105
5th week	1.34 ± 0.86	1.62 ± 0.60	0.000
6th week	1.03 ± 0.93	1.49 ± 0.63	0.000
7th week	0.81 ± 0.82	1.35 ± 0.66	0.073
8th week	0.75 ± 0.84	1.23 ± 0.70	0.042
9th week	0.53 ± 0.71	1.10 ± 0.68	0.174
13th week	0.50 ± 0.71	1.03 ± 0.72	0.325
17th week	0.50 ± 0.71	0.99 ± 0.75	0.524
21st week	0.47 ± 0.71	0.92 ± 0.78	0.790

Table 3. Comparison of Intensity of Pruritis Score in ASST Positive and ASST Negative Patients Receiving AST

Duration of Wheals	ASST Positive (n=32) Mean ± S.D.	ASST Negative (n=78) mean ± S.D.	P Value (between Groups)
Baseline	2.00 ± 0.00	2.21 ± 0.40	0.000
1st week	1.97 ± 0.17	2.15 ± 0.45	0.000
2nd week	1.94 ± 0.24	2.09 ± 0.46	0.055
3rd week	1.78 ± 0.49	1.92 ± 0.55	0.623
4th week	1.56 ± 0.66	1.65 ± 0.64	0.551
5th week	1.16 ± 0.80	1.40 ± 0.74	0.727
6th week	0.81 ± 0.78	1.21 ± 0.77	0.975
7th week	0.75 ± 0.76	1.12 ± 0.78	0.843
8th week	0.66 ± 0.74	0.96 ± 0.79	0.679
9th week	0.53 ± 0.71	0.85 ± 0.80	0.431
13th week	0.53 ± 0.71	0.81 ± 0.77	0.686
17th week	0.53 ± 0.71	0.81 ± 0.77	0.686
21st week	0.50 ± 0.67	0.81 ± 0.77	0.373

Table 4. Comparison of Duration of Wheal Score in ASST Positive and ASST Negative Patients Receiving AST

Both ASST positive and negative groups showed improvement in intensity of pruritus score but the response was earlier in positive group. The difference in the intensity

of pruritus score between the two groups became significant in eighth week (p value 0.042). (Table-3).

The baseline value for duration of wheal score in both ASST positive and negative groups were comparable. Both groups showed improvement in duration of wheal score and the response was earlier in ASST positive group. (Table-4).

The baseline value for frequency of appearance of symptoms score in both ASST positive and negative groups were comparable .Both groups showed improvement in the score and the response was earlier in ASST positive group and the difference between the groups became significant in the fourth week (p value 0.047). (Table-5).

Frequency of Symptoms	ASST Positive (n=32) Mean ± S.D.	Asst Negative (n=78) Mean ± S.D.	P Value (between Groups)
Baseline	2.59 ± 0.49	2.72 ± 0.45	0.036
1st week	2.34 ± 0.48	2.47 ± 0.50	0.008
2nd week	2.09 ± 0.58	2.23 ± 0.50	0.802
3rd week	1.69 ± 0.59	1.92 ± 0.64	0.330
4th week	1.34 ± 0.48	1.41 ± 0.61	0.047
5th week	1.25 ± 0.44	1.27 ± 0.55	0.099
6th week	1.09 ± 0.46	1.19 ± 0.56	0.043
7th week	1.09 ± 0.46	1.10 ± 0.57	0.203
8th week	0.81 ± 0.69	1.04 ± 0.61	0.084
9th week	0.66 ± 0.70	0.99 ± 0.65	0.052
13th week	0.53 ± 0.67	0.87 ± 0.69	0.462
17th week	0.53 ± 0.67	0.85 ± 0.68	0.492
21st week	0.50 ± 0.67	0.76 ± 0.70	0.918

Table 5. Comparison of Frequency of Appearance of Symptoms Score in ASST Positive and ASST Negative Patients Receiving AST

The baseline value for frequency of use of antihistamines score in both ASST positive and negative groups were comparable. Both groups showed improvement in the score and the response was earlier in ASST positive and the difference between the groups became significant in the sixth week (p value 0.013). (Table-6).

Frequency of Use of Antihistamines	ASST Positive (n=32) Mean ± S.D.	ASST Negative (n=78) Mean ± S.D.	P Value (between Groups)
Baseline	2.53 ± 0.50	2.67 ± 0.47	0.061
1st week	2.28 ± 0.45	2.40 ± 0.49	0.011
2nd week	2.06 ± 0.61	2.14 ± 0.52	0.505
3rd week	1.53 ± 0.67	1.73 ± 0.67	0.733
4th week	1.19 ± 0.59	1.27 ± 0.55	0.862
5th week	0.97 ± 0.69	1.19 ± 0.53	0.307
6th week	0.69 ± 0.69	1.12 ± 0.58	0.013
7th week	0.66 ± 0.70	1.01 ± 0.63	0.016
8th week	0.63 ± 0.70	0.91 ± 0.68	0.145
9th week	0.47 ± 0.67	0.79 ± 0.70	0.852
13th week	0.44 ± 0.66	0.71 ± 0.72	0.620
17th week	0.41 ± 0.66	0.68 ± 0.71	0.495
21st week	0.41 ± 0.66	0.62 ± 0.72	0.324

Table 6. Comparison of Frequency of Use of Antihistamines Score in ASST Positive and ASST Negative Patients Receiving AST

It was observed that both ASST positive and ASST negative patients receiving AST showed a sustained decrease in their TSS. The decrease in TSS was more in ASST positive group compared to ASST negative group but the difference was not statistically significant (p value >0.05). Baseline, first week, 21st week TSS in the ASST positive patients were 14.78 ± 1.36, 13.81 ± 1.73, 3.00 ± 4.02 respectively and 15.12 ± 1.21, 14.17 ± 1.61, 4.75 ± 4.30 respectively in ASST negative patients.

Assessment of Response to Autologous Serum Therapy in ASST Positive and ASST Negative Patients

Out of 32 ASST positive patients 20 (62.5%) showed significant response whereas out of 78 ASST negative patients 32 (41%) showed significant response. 8 patients in ASST positive patients showed moderate response and 25 patients in ASST negative patients showed moderate response. Only 4 (12.5%) out of 32 ASST positive patients showed poor response compared to 25 (22.7%) in the ASST negative patients.

Out of the 19 ASST positive patients who showed significant response, 5 (26.3%) showed significant response by 5th and 6th week. Out of the 9 ASST positive patients who showed moderate response, 3 (33.3%) showed moderate response by 7th week. Out of 32 ASST positive patients, 4 (12.5%) was evaluated till 21st week and we found that the response to AST was poor.

Out of the 32 ASST negative patients who showed significant response, we found that maximum number of patients 7 (21.9%) showed significant response by 9th week. Out of the 25 ASST negative patients who showed moderate response, we found that maximum number of patients 8 (32%) showed moderate response by 7th week. Out of the total 72 ASST negative patients 21 (26.9%) patients were evaluated till 21st week. Among them 19 showed some response with AST at different weeks but the reduction in their total severity score remained less than 50% of the baseline till 21st week. 2 (9.52%) of the patients showed no response.

DISCUSSION

This study was conducted with an aim to evaluate the effectiveness of AST in both ASST positive and ASST negative patients with chronic idiopathic urticaria.

In our study, the youngest patient was a 13 year old male and the oldest was 63 year old male. Most of our patients belong to the fourth decade with mean age being 36.17 years which was in concordance with Krupashankar et al study[8] in which the average age observed was 35.36 years. Colgecen et al[9] also observed a mean age of 37.15 years in their study.

In our study, females outnumbered males (72 females and 38 males) with a male: female ratio 1:1.9 which was in concordance with studies conducted by Vohra et al[6] and Bakes et al[10] who noticed a male: female ratio of 1:2.2 and 1:1.6 respectively. This may be due to the higher incidence of autoimmune diseases in females.

The mean age in ASST positive group was 35.03 years and in ASST negative group was 36.64 years similar to the observation made by Yadav et al[11] where the mean age in ASST positive group was 32.5 years and ASST negative group was 33 years.

In our study, among the 110 patients evaluated 32 patients (29.1%) were found to be ASST positive and 78 (70.9%) were ASST negative which was comparable with the study conducted by Patil et al[12] where he found 26.6%

of patients as ASST positive but slightly lower than the percentage of ASST positivity observed in the studies by Vohra et al[6] (46%) and Bakos et al[10] (54%).

We observed thyroid antibody positivity in 46.9% of patients who were ASST positive compared to 10.3% in ASST negative group which was statistically significant and was in concordance with the study by Bakos et al[10] where thyroid antibody positivity was seen in 42.3% of patients who were ASST positive.

Among the 110 patients we evaluated, diabetes mellitus was found to be the commonest associated disease in 19 (17.3%) which was similar to the observation made by Krupashanker et al[8] where he found diabetes as the commonest associated disease (6.5%). Out of 23 patients who were thyroid autoantibody positive 13 patients were euthyroid.

The aim of our study was to evaluate the effectiveness of AST in both ASST positive and ASST negative patients with chronic idiopathic urticaria. In our study all the patients well tolerated AST and none of them experienced any untoward side effects. In the study done by Bajaj et al[4] soreness at the site of injection was noted by the patients which lasted for 12-24 hours.

In both ASST positive and ASST negative patients, the total severity score was comparable at baseline; for ASST positive 14.78 ± 1.36 and for ASST negative 15.12 ± 1.21 (p value- 0.285). Improvement in urticarial symptoms and TSS was observed in both ASST positive as well as ASST negative patients who received AST in the study done by Chopra et al.[13]

In the study done by Bajaj et al,[4] the mean TSS decline was faster and dramatic in the ASST positive group during the treatment phase than the ASST negative group though the difference was statistically not significant at the end of follow up. This pattern was observed in our study as well. Mean value at baseline in ASST positive (14.78 ± 1.36) and ASST negative (15.12 ± 1.21) which showed a sustained reduction in the successive weeks of treatment.

The evaluation of 110 patients in our study showed gradual reduction in all 6 parameters for both ASST positive and ASST negative group till the end of follow up period.

The reduction in the number of wheals score and size of wheals score in the ASST positive and ASST negative group became statistically significant in the 6th week with p value of 0.028 and 0.035 respectively and the reduction in the intensity of pruritus score became statistically significant in the 8th week with p value 0.042. Similarly the reduction of frequency of symptoms score between the groups became statistically significant in the 4th and 6th week with p values of 0.047 and 0.043 respectively. The reduction in frequency of antihistamine use in ASST positive and ASST negative group became significant in the 2nd week with p value 0.011. On subsequent weeks of follow up, we observed a gradual reduction of the scores in both groups but the difference was not statistically significant.

In our study all 6 individual parameters showed better and earlier response to AST in ASST positive patients than in ASST negative patients which was consistent with the studies done by Abd El Azim[14] and Bajaj et al.[4] In Debbarman et al[15] study, they found both the ASST positive and ASST negative groups benefitted from therapy but those patients with positive ASST required more time to experience the benefit of AST than ASST negative patients which was in contradiction to our observations.

Out of 32 ASST positive patients 20 (62.5%) showed significant response whereas out of 78 ASST negative patients 32 (41%) showed significant response. Only 4 (12.5%) out of 32 ASST positive patients showed poor response compared to 25 (22.7%) in the ASST negative patients.

CONCLUSIONS

Autologous serum therapy is a safe and effective mode of treatment in the management of chronic idiopathic urticaria. ASST positive as well as negative patients showed response to AST but it tends to be more effective and earlier in ASST positive patients. Various associations seen in our study indicate that a detailed history and thorough clinical examination is mandatory in evaluating a case of chronic urticaria. Higher prevalence of anti-thyroid antibodies and diabetes mellitus in our study points towards the need for TFT and thyroid antibody testing and blood sugar estimation in all cases of chronic idiopathic urticaria.

Financial or Other Competing Interests: None.

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