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The Turkish experience with therapeutic plasma exchange: A national survey

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ABSTRACT

Therapeutic plasma exchange (TPE) is used to treat more than 60 diseases worldwide and has drawn growing interest. Little is known about the current situation of TPE activity in Turkey, so we developed a survey to obtain information about this timely topic. We collected data on TPE from 28 apheresis units throughout Turkey. We performed a total of 24,912 TPE procedures with 3203 patients over the past decade. Twenty years ago, the majority of procedures were performed for neurological and hematological disorders, and today, most TPE procedures are done for the same reasons. The only historical change has been an increase in TPE procedures in renal conditions. Currently, renal conditions were more frequently an indication for TPE than rheumatic conditions. Fresh frozen plasma was the most frequently used replacement fluid, followed by 5% albumin, used in 57.9% and 34.6% of procedures, respectively. The most frequently used anticoagulants in TPE were ACD-A and heparin/ACD-A, used with 1671 (52.2%) and 1164 (36.4%) patients, respectively. The frequency of adverse events (AEs) was 12.6%. The most common AEs were hypocalcemia-related symptoms, hypotension, and urticaria. We encountered no severe AEs that led to severe morbidity and mortality. Overall, more than two thirds of the patients showed improvement in the underlying disease. Here, we report on a nationwide survey on TPE activity in Turkey. We conclude that there has been a great increase in apheresis science, and the number of TPE procedures conducted in Turkey has increased steadily over time. Finally, we would like to point out that our past experiences and published international guidelines were the most important tools in gaining expertise regarding TPE.

1. Introduction

According to the seventh edition of guidelines published by the American Society for Apheresis (ASFA) in 2016, therapeutic plasma exchange (TPE) is a procedure in which a specific blood component is selectively removed from the patient using a medical device and then replaced with another solution, such as a colloid solution (e.g., albumin and/or plasma) or a combination crystalloid/colloid solution [1]. This method makes possible the removal of pathological substances, such as antibodies, immune complexes, cryoglobulins, immunoglobulin light chains, cytokines, adhesion molecules, and endotoxins, while also allowing the replacement of missing plasma components [2]. This treatment achieves dramatic responses in various conditions, especially some forms of thrombotic microangiopathies [3]. The indications for TPE have changed over time due to growing data obtained by evidence-based applications. In the present study, retrospective information was collected on TPE carried out throughout Turkey. We also share our experiences using TPE with a wide variety of disorders, highlighting its efficacy and safety.

2. Material and methods

Therapeutic apheresis centers in Turkey record all the demographic data for each patient and the clinical and analytical data for each TPE procedure. Before TPE procedures are started, patients are evaluated strictly to ensure the accuracy of TPE indications, chronic illnesses, and current medications, particularly angiotensin-converting enzyme inhibitors and beta-blockers. In routine practice, a signed informed consent is obtained from patients or their relatives before the procedure and its related risks and benefits are explained. Then, a trained staff member (an apheresis technician or an apheresis nurse) evaluates peripheral venous access to determine whether it is suitable to perform the TPE procedure. In some instances, an arteriovenous fistula, when present, is considered as peripheral venous access. If needed, an indwelling catheter is placed by trained personnel. Laboratory assays, including complete blood counts, coagulation, and biochemistry parameters, are evaluated immediately before starting and after finishing each TPE procedure. The patient's clinical, medical, and laboratory status determine the type of anticoagulant and replacement fluid. In addition to procedural data, responses to TPE and adverse events (AEs) are recorded in the apheresis unit's database. Of note, under Turkish regulations, TPE should be conducted by trained apheresis technicians or nurses supervised by a specialist physician in hematology [4].

In the present study, adult patients older than age 16 years who underwent TPE between January 1, 2007, and December 31, 2017, were evaluated through a retrospective review of records from 28 therapeutic apheresis centers. The following data were collected using a detailed form: the patient's age, sex, chronic illnesses, TPE indication, vascular access site, treated plasma volume, total TPE sessions, replacement fluid and anticoagulant used, treatment outcomes, and AEs during the procedure. Other therapeutic apheresis applications were not recorded, and data from pediatric apheresis units were not part of this study.

The definition of responses could vary with the underlying disease, so the researchers used common terminology. The clinical outcomes of the patients who underwent TPE were categorized as complete response (CR), partial response (PR), or no response. CR was defined as the disappearance of all presenting symptoms and normalization of the laboratory values. PR was defined as achievement of at least 50% normalization in laboratory values compared to initial status and no new clinical events. No response was defined as stable disease (clinically and laboratory) or deterioration of the patient's clinical status despite proper TPE.

All statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). The continuous variables were summarized with descriptive statistics (median, minimum, and maximum), and the categorical variables were summarized in frequency tables.

3. Results

The study population comprised 3203 patients, including 1580 (49.3%) men and 1623 (50.7%) women, with a median age of 49 years (range: 16–96 years) and 44 years (range: 16–96 years), respectively. We performed a total of 24,912 TPE procedures with 3203 patients, for a median of 5 treatments per patient (range: 1–100). According to ASFA guidelines, the majority of the indications belonged to category I and category II (Table 3). The five most common indications for TPE were thrombotic thrombocytopenic purpura (TTP), renal transplantation ABO incompatible, hyperviscosity in monoclonal gammopathies, myasthenia gravis (MG), and acute inflammatory demyelinating polyneuropathy/Guillain-Barre syndrome (AIDP/GBS) (Table 1). The distribution of the patients and TPE procedures is given by year in Fig. 1. The collected data on TPE are separated into four general diagnostic categories to illustrate the general trends of use (Fig. 2). These major indications subject to TPE are shown in Fig. 2. The current situation of TPE activity in Turkey is displayed by year in Fig. 3. The number of

Table 1
The technical notes of therapeutic plasma exchange procedures.

Parameters	Values
Total number of patients, female to male	3203 (1623/1580)
Five most indications, n (%)	
- Thrombotic thrombocytopenic purpura	502 (15.7)
- Renal transplantation, ABO incompatible	390 (12.2)
- Hyperviscosity in monoclonal gammopathies	289 (9.0)
- Myasthenia gravis	210 (6.6)
- Guillain-Barre syndrome	174 (5.4)
Total number of procedures	24912
Number of procedures per patient, median (range; min-max)	5 (1-100)
Duration of procedure (minutes), median (range; min-max)	100 (16-450)
Frequency of procedure, n (%)	
- Daily	1782 (55.6)
- Every other day	1183 (36.9)
- Once a week	57 (1.8)
- Twice weekly	58 (1.8)
- Three times a week	47 (1.5)
- Other	76 (2.3)
Plasma volume treated (x PV), n (%)	
- 1	2131 (66.5)
- 1.5	998 (30.8)
- 2	84 (2.6)
Venous access, n (%)	
- Peripheral vein	508 (15.9)
- Central venous catheter	2607 (81.4)
- Arterio-venous fistula	88 (2.7)
Anticoagulant, n (%)	
- ACD-A	1671 (52.2)
- Heparin	368 (11.5)
- Heparin / ACD-A	1164 (36.3)
Replacement fluid, n (%)	
- FFP (fresh frozen plasma)	1856 (57.9)
- 5% Albumin	1109 (34.6)
- HES (hydroxyethyl starch)	31 (1.0)
- HES plus 5% Albumin	1 (0.0)
- FFP plus 5% Albumin	206 (6.4)
- SDP (solvent detergent plasma)	0 (0.0)
Apheresis device*	Spectra Optia / Fresenius
Responses, n (%)	
- Complete remission	1973 (61.6)
- Partial remission	718 (22.4)
- No response	512 (16.0)

* The most two devices used.

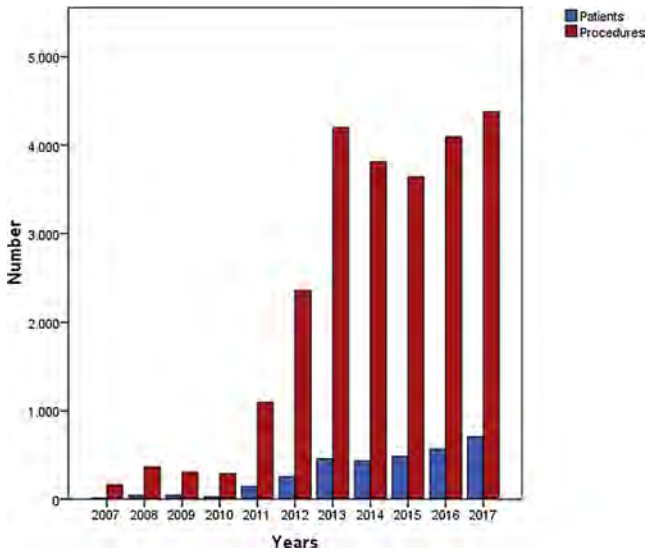

Fig. 1. The distribution of the patients and TPE procedures by year.

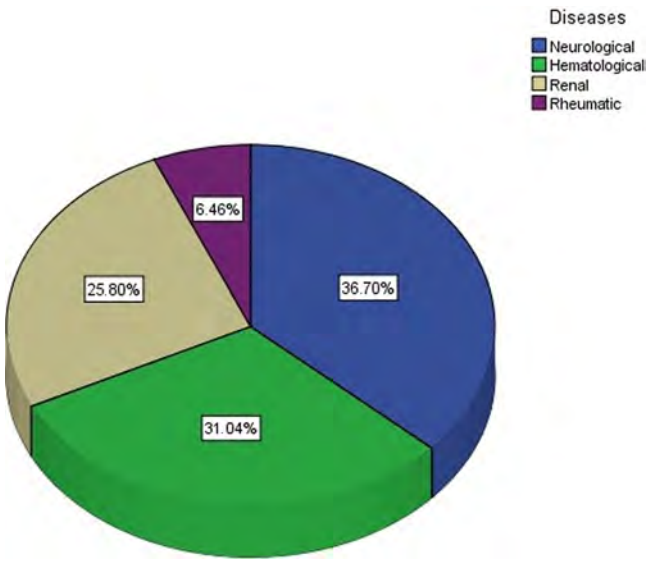

Fig. 2. The four major indications subject to TPE.

indications subject to TPE in this study was more than 50; however, we did not display all of them because the number of procedures for some indications was limited.

The technical notes of the procedures are displayed in Table 1. The TPE procedures were performed using various apheresis devices, most commonly the Spectra Optia and Fresenius. Most procedures were carried out daily or every other day (Table 1). Fresh frozen plasma (FFP) was the most used replacement fluid in 57.9% of procedures, followed by 5% albumin in 34.6% of procedures. The vascular access site was central lines and peripheral veins in 81.4% and 15.9% of procedures, respectively. The most frequently used anticoagulants in TPE were ACD-A and heparin/ACD-A with 1671 (52.2%) and 1164 (36.4%) patients, respectively. Due to the wide variety of the conditions subject to TPE, data on adjuvant treatment modalities were not analyzed in this study.

We observed 407 (12.6%) AEs during TPE procedures (Table 2). Of the AEs, hypocalcemia-related symptoms, hypotension, and urticaria were the most frequent. Procedural-related AEs were most frequent in cases of AIDP/GBS (19%), TTP (18.3%), and MG (17.1%). All these AEs were mild in severity and managed with proper methods. Severe reactions were much less common, and no deaths were reported. The outcomes of the patients treated with TPE are shown in Table 1. Overall, more than two thirds of the patients showed improvement in the underlying disease (Table 1). Definitive evidence of the benefits of TPE in the study patient population (CR rate ≥ 60%) is displayed in Table 3.

4. Discussion

Although TPE is performed for a broad spectrum of conditions, there is no international consensus on clear-cut guidelines for clinicians. Nevertheless, organizations, such as the ASFA, European Society for Hemapheresis, American Association of Blood Banks, and Canadian Apheresis Group (CAG), regularly publish evidence-based guidelines for TPE to make informed decisions [5]. The Turkish Ministry of Health in Turkey published its first Therapeutic Apheresis Regulation in March 2010 [4,6,7]. The first Turkish Apheresis Centers Guide was published that same year to set standards throughout the country [6–8]. Since then, remarkable progress has been made in apheresis science in Turkey due to efforts by the Turkish Society of Apheresis. In 1998 and 2011, there were 31 and 53 apheresis units in Turkey, respectively, and today, the number of units exceeds 70 [6,7]. As of 2015, the Turkish Ministry of Health had certified 12 therapeutic apheresis units as education

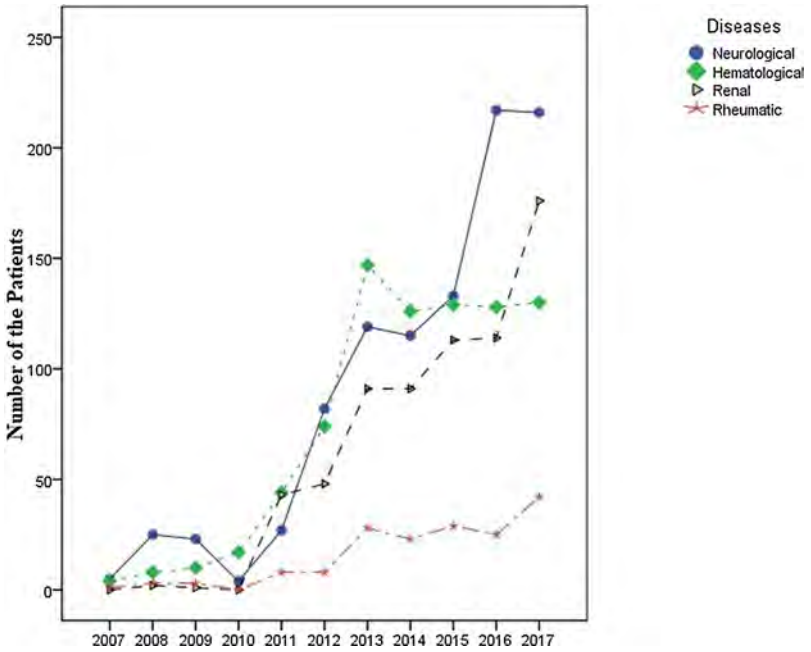

Fig. 3. The current situation of TPE activity in Turkey by year.

Table 2
Procedure related adverse events.

Adverse event	n (%)
Catheter dysfunction	46 (1.4)
Hypocalcaemia related symptoms	83 (2.6)
Hypotension	80 (2.5)
Urticaria	68 (2.1)
Nausea	16 (0.5)
Vomiting	7 (0.2)
Cardiac arrhythmia	8 (0.2)
Fever	19 (0.6)
Respiratory distress	13 (0.4)
Cardiac arrest	0 (0.0)
Hypertension	67 (2.1)
Death	0 (0.0)
No complication	2796 (87.4)

centers for apheresis [6].

In 1998, 21 centers in Turkey performed 869 TPE procedures for 172 patients mostly to treat TTP and aHUS (now called complement-mediated thrombotic microangiopathy) [9]. The most frequent indications for TPE were neurological and hematological diseases, as in our study. There has been growth and changes in practice in renal conditions over the years, and today, renal conditions are more frequent indications for TPE. Over the years, the annual total number of TPE procedures in Turkey has increased substantially compared to reports on other apheresis groups [10–14]. Nevertheless, Turkey lags behind CAG, the pioneer group in this field and the largest TPE registry which regularly reports 8000 procedures annually [15–17]. In our study, 7973 procedures were carried out to treat TTP in 502 patients using FFP. As well, 2405 procedures for 390 patients with renal transplantation ABO incompatible, 1434 procedures for 289 patients with hyperviscosity in monoclonal gammopathies, 1451 procedures for 210 patients with MG, and finally, 975 procedures for 174 patients with AIDP/GBS were performed to great success.

Table 3
The definitive evidence of benefit of TPE in our patient population (CR rate ≥ 60%).

Patient population	Number of patients	Number of procedures	ASFA 2016 category	CR n (%)	PR n (%)	No response n (%)
Neurological diseases						
-Myasthenia gravis	210	1451	I	141 (67.1)	46 (21.9)	23 (11)
-Guillain-Barre syndrome	174	975	I	122 (70.1)	35 (20.1)	17 (9.8)
-Neuromyelitis optica spectrum disorders	69	421	II	46 (66.7)	17 (24.6)	6 (8.7)
-Chronic inflammatory demyelinating polyradiculoneuropathy	15	92	I	9 (60)	6 (40)	0 (0.0)
Hematologic diseases						
-Thrombotic thrombocytopenic purpura	502	7973	I	385 (76.7)	39 (7.8)	78 (15.5)
-Hyperviscosity in monoclonal gammopathies	289	1434	I	190 (65.7)	76 (26.3)	23 (8)
-Myeloma cast nephropathy	55	219	II	33 (60)	19 (34.5)	3 (5.5)
-Hematopoietic stem cell transplantation, ABO Incompatible	37	73	II	36 (97.3)	1 (2.7)	0 (0.0)
-Severe cold agglutinin disease	26	136	II	19 (73.1)	6 (23.1)	1 (3.8)
-Autoimmune hemolytic anemia; WAIHA	12	65	III	8 (66.7)	2 (16.7)	2 (16.7)
-Thrombotic microangiopathy, drug associated	8	109	I / III	5 (62.5)	3 (37.5)	0 (0.0)
Renal diseases						
-Renal transplantation, ABO incompatible	390	2405	I / II	269 (69)	85 (21.8)	36 (9.2)
- Focal segmental glomerulosclerosis	55	429	I	41 (74.5)	11 (20.0)	3 (5.5)
-Goodpasture's syndrome	26	248	I	16 (61.5)	1 (3.8)	9 (34.7)
Rheumatic diseases						
-Vasculitis	93	717	II / III	56 (60.2)	19 (20.4)	18 (19.4)
-Systemic lupus erythematosus	64	433	II	39 (60.9)	15 (23.4)	10 (15.7)

TPE for neurological diseases has increased each year, and today, these remain the most common indications for TPE in Turkey. Currently, MG is the most frequent neurological indication for TPE, followed by AIDP/GBS, while multiple sclerosis is the third most common indication for TPE. Use of TPE in patients with multiple sclerosis has decreased in recent years due to demonstrated lower CR rates (43.9%). Nevertheless, it seems likely that treatment of neurological diseases will continue to be an active area in TPE.

Hematologic indications were the second most common reason for TPE and have remained stable since 2014. TTP and hyperviscosity in monoclonal gammopathies were the most common hematologic indications. Use of TPE for complement-mediated thrombotic microangiopathy (formerly called atypical hemolytic syndrome) has decreased due to the availability of eculizumab (anti-C5 monoclonal antibody) and the minimal benefit of the procedure.

Interestingly, renal diseases have increased since 2011 and become the third most common indications for TPE. In 1998, renal diseases accounted for 1% of indications for TPE in Turkey [9]. Today, renal diseases account for approximately 26% of all TPE indications and rose to second place as of 2017. This trend is similar in reports from other apheresis groups [11,12]. Renal transplantation 'ABO incompatible' and focal segmental glomerulosclerosis were the most common reasons for TPE related to renal diseases. Antibody-mediated rejection was the main reason for TPE in renal transplantation patients, and desensitization was another reason in a small subset of the sample. Goodpasture's syndrome, particularly among patients with pulmonary hemorrhage, was the third most common TPE indication related to renal diseases.

Rheumatic diseases were the least common indications for TPE. Vasculitis and systemic lupus erythematosus were the most common reasons for TPE related to rheumatic diseases. The other rheumatic diseases, such as catastrophic antiphospholipid syndrome and scleroderma (systemic sclerosis), were rarely indications for TPE but did not disappear.

Under ASFA guidelines, the majority of the indications in our study belonged to category I and category II. Today, the number of procedures for ASFA category IV indications has decreased almost to zero. Our results suggest that patient selection and ASFA categorization in this study are similar to those in reports on many other apheresis groups [10,12,14–16,18,19].

An interesting finding in our study is snake-venom poisoning as an indication for TPE. Envenomation by snakes (Anatolian vipers), especially in the summer, is frequent in eastern and southeastern Anatolia in Turkey. In our study, there were 20 envenomation cases. Some apheresis centers in these areas used TPE for this indication and showed that TPE demonstrated an excellent CR rate (100%) and saved many lives. Data on TPE for envenomation have been accumulated worldwide, so the category of envenomation might change over the years.

TPE can be performed using either centrifugation-based or filtration-based devices. In the past decade, most apheresis units in Turkey have moved to use apheresis devices capable of continuous-flow centrifugation instead of intermittent-flow centrifugation. The remaining centers still prefer filtration-based devices over centrifugation-based devices. In addition to apheresis devices, vascular access plays a key role in successful treatment. In our study, vascular access exclusively at central veins accounted for more than 80% of the procedures. Arteriovenous fistula was not a common practice unlike in a French national survey on TPE [20].

TPE procedures varied in the frequency of sessions, treated plasma volume per session, type of replacement fluid used and anticoagulation according to the underlying disease. In a typical TPE procedure, an average of 1.0–1.5 plasma volumes were removed from the patient and replaced with fluid. The replacement fluids most frequently used in Turkey were FFP and albumin. HES has been associated with more frequent urticarial and pruritic reactions than albumin and may result in coagulopathy, so it is used less than other replacement fluids [17]. There is no doubt that TPE is a valuable treatment modality; however, it is a complex and expensive procedure. The average cost of a TPE procedure in Turkey is $520 when using FFP and $800 when using albumin as replacement fluid. These costs are similar to those reported by other apheresis groups [14,16]. Considering the extra burden of treatment costs, Turkey, as a developing country, should develop management policies to reduce costs.

AEs can be expected to occur in 12% of procedures [21]. In our study, the frequency of AEs was 12.6%, and the most frequent AEs were hypocalcemia-related symptoms, hypotension, urticaria, and catheter dysfunction. The frequency of AEs observed was 3% in another study [3] and 5.7% in the World Apheresis Association registry [22]. The risk of AEs was higher in patients receiving FFP as the replacement fluid, so our slightly higher results could be attributed to FFP and may have been medication related in some instances. However, severe reactions were much less common, and none led to mortality or treatment discontinuation as a result of TPE, similar to the results of other studies [23,24]. AEs were managed by temporarily halting the procedure, giving saline infusions, decreasing the blood inflow rate, and slowing infusion of intravenous calcium, as indicated. We would like to point out that calculating the infusion of calcium and magnesium delivered intravenously throughout a procedure was not a common practice in Turkey, and most AEs were related to hypocalcemia. A reasonable solution, therefore, might be prophylactic infusion of calcium with or without magnesium throughout TPE sessions and the selection of an appropriate anticoagulant for the underlying disease. Of note, the underlying disease, current medications, and various TPE technical parameters need to be considered, particularly for patients on anticoagulant medications, to avoid risk of hemostatic complications, such as bleeding and clotting [25–27].

Our trial shows definitive evidence of benefits from TPE in the treatment of various disorders. TPE was of benefit in treating neurological diseases, such as AIDP/GBS, MG, and neuromyelitis optica, as in other studies [11,16,28]. TTP is a life-threatening disorder and, if untreated, has a mortality rate higher than 90% [15,29,30]. We observed significant benefits for patients with TTP, who experienced a 76.7% CR rate in this study. Focal segmental glomerulosclerosis among renal diseases and systemic lupus erythematosus among rheumatologic diseases were the conditions that most benefitted from the procedure. Despite these encouraging results, we encountered 16% of treatment failures without any mortality, a comparable rate to other studies [3,13,31–33].

The study results are subject to some limitations. The main limitation is the retrospective study design. As well, the study did not include data from pediatric apheresis units, and apheresis units active in this field could not participate due to the short data collection period. Moreover, we would like to state that about one-third of the apheresis centers in Turkey perform mostly component collection rather than TPE. Finally, data on adjuvant treatment modalities are not included in this study due to the wide variety of conditions subject to TPE. Nevertheless, we conclude that this survey is representative of TPE activity in Turkey as we collected homogenous data from throughout the country.

In summary, TPE is a valuable treatment modality for many established diagnoses; however, not all indications for TPE are clinically supported as beneficial. TPE performed by trained personnel is a safe, effective therapeutic approach when applied in the conditions most likely to facilitate benefits from the treatment. Follow-up to worldwide established guidelines and updates to national regulations are needed to manage patients who need TPE. We conclude that continuing education, standardization efforts, and collaboration at Turkish centers have increased the number of therapeutic apheresis centers and therapeutic apheresis procedures performed per year, along with their quality, standardization, and success. Nevertheless, there is an urgent need to establish a Turkish TPE national registry to organize multi-institutional study groups to carry out clinical trials to determine annual TPE activity

and obtain more accurate, comprehensive data to suggest appropriate clinical applications.

Conflicts of interest

none

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