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Tolerance and complications of therapeutic plasma exchange by centrifugation: a single center experience

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ABSTRACT

Introduction. Therapeutic plasma exchange (TPE) constitutes an important therapy for hematological, neurological, immunological, and nephrological diseases. Most studies have focused on efficacy, whereas tolerance and complications during sessions have been less well studied and not recently.

Material and Methods. We conducted a single center retrospective study of all patients who underwent TPE between 2011 and 2018. TPE sessions using the centrifugation technique were performed by dedicated trained nurses. Specific side effects were identified through surveillance forms completed contemporaneously. The primary outcome was the rate of all-type adverse effects that occurred during the TPE sessions.

Results. In total, 1,895 TPE sessions performed on 185 patients were analyzed. At least one adverse effect was reported for 805 sessions (42.5% [29.9%–70.1%]), corresponding to 171 patients (92.4% [87.6%–95.8%]). Hypotension occurred during 288 sessions (15.2%), was asymptomatic in 95.8% of cases, and more frequent with the use of 4% albumin than fresh frozen plasma (FFP) (19.8 versus 8.9%, $p < 0.0001$). Hypocalcemia occurred during 370 sessions (19.6%) and was more frequent with the use of FFP than with the use of albumin alone (FFP alone: 28.0%, albumin + FFP: 26%, albumin alone: 11.7%; $p < 0.0001$). Allergic reactions occurred during 56 sessions (3%), exclusively with FFP. Severe adverse effects were reported for 0.3% of sessions and 5.4% of patients.

Conclusions. TPE is a safe therapy when performed by a trained team. Adverse effects were frequent but mostly not serious. The replacement fluid was the main determinant of the occurrence of complications. (ClinicalTrials.gov ID: NCT03888417).

Keywords: therapeutic plasma exchange, fresh frozen plasma, albumin, hypotension, hypocalcemia, allergic reaction.

List of abbreviations: A: albumin, A+FFP: albumin + fresh frozen plasma, ACD-A: acid citrate dextrose, solution A, EPV: estimated plasma volume, FFP: fresh frozen plasma, HES: hydroxyethyl starch, ICU: Intensive Care Unit, TPE: therapeutic plasma exchange, UERTU: Urgent Extracorporeal Replacement Therapy Unit.

INTRODUCTION

Therapeutic plasma exchange (TPE) was first utilized in human medicine at the end of the 1950s (1). Since then, the efficacy of TPE has been well evaluated (2-5) and international recommendations and the levels of evidence are frequently updated (6). TPE is currently recommended as first- or second-line therapy for approximately 20 disorders, with high-quality evidence for only four of them.

The mechanism of action of TPE is not completely understood (7). It is largely accepted that two main elements are the removal of pathological substances from the blood (8) and/or the replacement of deficient plasma components (9). TPE is currently performed using either a high-permeability filter with standard multifunctional renal replacement equipment or a centrifugation device (10).

Most authors have used national registries to report complications associated with TPE procedures (11-13) and described complications associated with various types of apheresis (TPE, cytapheresis, LDL-adsorption). Registries have the advantage of gathering multicenter observational data. However, such studies do not guarantee completeness because data collection is heterogeneous between centers. Moreover, the various plasmapheresis techniques used were generally not described. We assessed the type and frequency of adverse effects during TPE performed by a dedicated staff using a standardized protocol.

MATERIALS AND METHODS

Study design and patients

We conducted a single center retrospective observational study at the Rennes University Hospital between January 2011 and December 2017. Eligibility criteria were being an adult and having had at least one TPE session during the study period. Patients under legal

protection, minors, those who declined to participate in the study, and those for whom monitoring forms were not found were not included. The study protocol was approved by the Rennes Hospital Institutional Review Board (agreement number 18.59) before the beginning of the study.

TPE sessions

The TPE sessions were performed by nurses specifically trained in the TPE technique in the Urgent Extracorporeal Replacement Therapy Unit (UERTU) of the Infectious Diseases and Medical Intensive Care Department. Procedures were generally performed in the Intensive Care Unit (ICU) TPE room within the Medical Intensive Care Department. Most patients hospitalized in other wards were transferred to the TPE room for the TPE treatment except for critically ill patients in other ICUs, for whom TPE was performed on site. The indications and number of sessions were decided according to international recommendations (6), in agreement with the patients' specialist physician and the TPE referent intensivist. The nature of the replacement fluid depended on the indication, the bleeding risk, and the interval between TPE sessions. The type and number of fresh frozen plasma (FFP) units were provided by the French Blood Establishment (Établissement Français du Sang), depending on available stocks. When 4% albumin (A) was used as the replacement fluid, a small proportion of hydroxyethylstarch (HES) was included at the beginning of the TPE session, as recommended (14, 15).

The plasmapheresis technique used in our center was exclusively centrifugation, regardless of the indication. It was chosen because of the higher efficiency of plasma extraction relative to filtration (16) and the possibility of using peripheral venous access. The device used was the Comtec Cell Separator (Fresenius Kabi - 61352 Bad Homburg, Germany). Anticoagulation of the extracorporeal circuit was achieved using acid citrate dextrose solution A (ACD-A). The

total volume of ACD-A used during the procedure and the volume reinfused to the patient were calculated by the centrifuge. Hypocalcemia was prevented by continuously infusing calcium during the TPE procedure, the amount based on the measurement of prior ionized calcium levels and the type of replacement fluid used. Generally, 2 g calcium gluconate per hour was infused with A and 2 g calcium chloride per hour with FFP.

The choice of venous access depended on the indication for TPE, the number of sessions planned, the patient's status, and the condition of the peripheral veins of the upper limbs. Ultrasound-guided insertion of a dialysis catheter at the jugular or subclavian site was systematically checked by chest x-ray to ensure proper positioning and the absence of any complication (e.g. pneumothorax).

Standardized monitoring forms were designed for the surveillance of TPE sessions and were contemporaneously completed by the nurses. (*Supplementary material 1*).

Data collection

Patient characteristics were collected, including age, height, weight, and TPE indication. Cardiorespiratory monitoring parameters during sessions were recorded (blood pressure, heart rate, pulse oximetry, and respiratory rate), as well as data related to the TPE procedures (volumes processed and treated, nature and site of venous access, hypocalcemia or anaphylaxis symptoms, ACD-A volume used, dose of calcium infused, device-related problems, discontinuation of the session, and any other event considered to be an adverse effect). Biological data collected included ionized calcium levels, pH, and hematocrit. Ionized calcium and pH were measured in whole blood. Bacteriological results of the catheter culture were collected, as well as all blood cultures performed during the treatment period.

Adverse effects: definitions and classifications (*Supplementary Material 2*)

Hypotension was defined as the occurrence of a mean arterial pressure <65 mmHg and/or a decrease in systolic arterial pressure >30 mmHg during the session relative to baseline and was classified into three severity grades. Hypocalcemia was diagnosed if the ionized calcium level was <1.10 mmol/L. The severity of hypocalcemia was determined according to the Lee classification (17). Allergic reactions were classified from grade I to IV according to the Ring and Messmer classification (18).

Among complications associated with venous access (pain, bleeding at the catheter insertion site and dysfunction of the catheter, the single-use kits, or the centrifuge) were identified from monitoring forms. Chest x-rays after insertion of the dialysis catheter at the superior vena cava site were examined to assure proper positioning and the absence of pneumothorax. Venous Doppler examination was performed if catheter-related thrombosis was suspected. The catheter tip was submitted for bacteriological culture if there was local inflammation or systemic signs. The diagnosis of infection related to venous access was performed in accordance with international recommendations (19). Cases with catheter-tip positive cultures were classified as catheter-associated bloodstream infection if the blood cultures were positive for the same microorganism or, otherwise, as catheter colonization.

Outcomes and statistical analysis

The main outcome was the rate of all-type adverse effects, expressed as the number (percent) of sessions and the number (percent) of patients. The rates of each type of adverse effect and overall severe adverse effects were secondary outcomes. Proportions were estimated with the 95% confidence interval (95% CI) by the method of Clopper and Pearson. Statistical analysis was performed using StatView 5.0 version, SAS. Quantitative variables were expressed as medians (25th percentile-75th percentile) and comparisons between groups were performed using the Mann Whitney U test or Kruskal-Wallis test. Categorical variables were compared

using the chi-square test or Fisher's exact test, as appropriate. All tests were two-sided and a p-value <0.05 was considered statistically significant. Post-hoc multiple comparisons between groups were performed according to the Bonferroni correction (a p-value <0.0167 was considered statistically significant for three comparisons).

RESULTS

Description of the population and TPE sessions

Session characteristics

In total, 185 patients were included, allowing the analysis of 1,895 TPE sessions (*Figure 1*). The main diagnosis was thrombotic microangiopathy syndrome (488 TPE sessions [25.8%] and 55 patients [29%]). Other diagnoses are listed in *Table 1*.

Of the 1,895 sessions, 452 (23.9%) were performed during an ICU stay, 903 (47.7%) during hospitalization in specialty departments, and 540 (28.5%) as outpatients. Venous access consisted of a dialysis catheter for 1,027 sessions (54.2%), mostly placed in the jugular vein (68.7%). The prescribed exchanged volume was 4,000 mL [3400–4600] or 55.9 mL/kg [50–61.5], representing a volume ratio (ratio of the exchanged volume to the estimated plasma volume [EPV]) of 1.3 [1.2–1.4] (*Table 2*). The exchanged volume varied depending on the TPE indication. A particularly large volume was prescribed for the treatment of acute liver failure (2.5 x EPV). Other characteristics of the sessions are reported in *Table 2*.

Replacement fluids

The replacement fluids used were FFP alone, 4% A alone, or a combination of 4% A and FFP (A+FFP) for 596 (31.5%), 933 (49.2%) and 366 (19.3%) TPE sessions, respectively (*Tables 1 and 2*). Among the total of 13,472 FFP units, four different types of FFP were delivered during the study period: either untreated quarantined units (38.9%) or pathogen-inactivated

units (amotosalen-inactivated: 24.6%, solvent/detergent-treated: 21%, methylene blue-treated: 15.5%). HES was given in 80.4% of sessions using A alone and 26.2% of sessions using A+FFP.

ACD-A and calcium use

The total volume of ACD-A used during the sessions (*Table 2*) was 559 mL [476–663] and the volume finally returned to the patient 129 mL [75–439]. This volume was substantially lower when the replacement fluid used was A (78 mL [63–106]) versus FFP (445 mL [378–518]) or A+FFP (417 mL [350–478]) (all $p < 0.0001$).

Description of adverse effects

At least one adverse effect was reported for 805 of the 1,895 sessions (42.5% [29.9%–70.1%]) and 171 of the 185 patients (92.4% [87.6%–95.8%]).

Hypotension

Hypotension occurred during 288 sessions (15.2% [13.6%–16.9%]) and was asymptomatic in 276 (95.8%) (*Table 3*). Hypotension was more frequent when 4% A alone was used as the replacement fluid (19.8% of sessions [17.3%–22.6%]) than when FFP (8.9% [6.7%–11.5%]) or A+FFP (13.7% [10.3%–17.6%], $p < 0.0001$) were used. HES was used during 847 sessions (65.2%) with A alone or A+FFP. Hypotension was more frequent when HES was initially used as a component of the replacement fluid (10.4% versus 22.2%, $p < 0.0001$; OR per 0.5 L HES fraction: 1.25 [1.11–1.42], $p = 0.0003$). Using A alone or A+FFP, the occurrence of hypotension during TPE session depended on the indication and was more frequent for chronic inflammatory demyelinating polyneuropathy (CIDP, 41.3%) and myasthenia gravis (MG, 28.5%) than for other diseases (13.9%, both $p < 0.0001$). In multivariate logistic regression analysis, CIDP (OR: 2.70 [1.73–4.22], $p < 0.0001$) and the use of HES (OR: 2.17 [1.42–3.31], $p < 0.001$) were associated with the occurrence of hypotension (*Table 4*).

Hypocalcemia

Hypocalcemia occurred during 370 of the 1,891 sessions (19.6% [17.8%–21.4%]) (*Table 3*). Among these cases, 270 (73%) were grade I (asymptomatic), 73 grade II (19.7%), and 25 grade III (6.8%). Two cases were severe (grade IV) and manifested by seizure (one patient) and hypotension and bradycardia (the other patient). Hypocalcemia was more frequent when FFP was used as the replacement fluid versus A (FFP: 28% [24.5%–31.9%], A+FFP: 26% [21.5%–30.8%], A: 11.7% [9.7%–13.9%], $p < 0.0001$).

Allergic reactions

An allergic reaction was observed in 56 of 1,890 sessions (3.0% [2.3%–3.8%]), exclusively with FFP as the replacement fluid (6.9% of FFP sessions [5.0%–9.3%], *Table 3*). Of the 56 reactions, 52 were grade I (93%), three were grade II, and only one was grade III (anaphylactic shock). There was an increasing risk of allergic reaction per liter of FFP infused (OR: 1.34 [1.11–1.63], $p = 0.003$).

The incidence of allergic reactions was significantly lower with the use of pathogen-inactivated FFP units (4.2%) than exclusively untreated quarantined FFP units (9.3%, $p = 0.002$), with a similar number of FFP units used in both settings (14 units [8–19] and 15 units [10–18] respectively, $p = 0.71$).

Other adverse effects

Digestive symptoms occurred during 34 sessions (1.8% [1.3%–2.5%]) and malaise during 11 (0.6% [0.3%–1.0%]). These symptoms were neither explained by hypocalcemia nor hypotension. Overall, oxygen had to be increased during 21 sessions (1.1% [0.7%–1.7%]), almost exclusively with FFP (3.2% [1.9%–4.9%], versus 0.3% [A+FFP] and 0.1% [A], $p < 0.0001$). Oxygen increase occurred during 1 of 56 (1.8%) sessions with and 20 of 1834

(1.1%) sessions without an allergic reaction ($P=0.47$). Overall, 25 sessions (1.3% [0.9–2.0]) were stopped prematurely (*Table 3*).

Non-infectious venous access-related complications

Among the 1,891 sessions analyzed, 202 adverse effects were associated with complications related to venous access (10.7% [9.3%–12.2]) (*Table 5*). Most (88.1%) consisted of dysfunction of the venous access (inverted lines or too low or too high venous pressure). The overall rate of complications and that of venous access dysfunction varied considerably, depending on the type of venous access (all $p<0.0001$), the highest frequencies of 19.3% (15.7%–23.3%) and 17.7% (14.2%–21.6%) occurring with the use of peripheral venous catheters (versus other types of venous access: 8.1% [7.4%–10.5%] and 6.9% [5.7%–8.3%], respectively; all $p<0.0001$).

Infectious venous access-related complications

Among 163 dialysis catheters used, 74 catheter tips (45.4%) were submitted for culture due to a suspected infection. There were five cases of catheter-related bacteremia (*Supplementary Material 3*), resulting in an incidence rate of 3.5‰ catheter-days (1.1‰–8.1‰). The incidence rate of catheter colonization was 11.5‰ catheter-days. *Staphylococcus epidermidis* was found in 13 of 17 cases of colonization (76%). There were no documented infections associated with the use of other types of venous access.

Severe adverse effects

Severe complications were those that were potentially life-threatening (grade III hypotension, grade III allergic reactions, and grade IV hypocalcaemia). Bacteremia was recorded as a patient-related rather than session-related complication. Severe complications were reported for 5 of 1895 sessions (0.3% [0.1–0.6%]) and 10 of 185 patients (5.4% [2.6–9.7%], including bacteremia).

DISCUSSION

This is the first recent study to reassess the adverse effects of TPE. Previous studies examined periods prior to 2010 (20), most often the late 1990s and early 2000s (21, 22). The most important result concerns the safety of TPE, which showed excellent clinical and biological tolerance (*Table 3*) and only rare severe adverse effects. The replacement fluid was the main determinant for the occurrence of adverse effects.

Hypotension was frequent, but largely asymptomatic or mild. A higher rate of hypotension with the use of A than that of FFP has already been reported by Shemin et al. (23). The mechanism is poorly understood, because the osmolarity of the two solutions is similar (24).

Severe hypotension during TPE has been reported in patients with acute inflammatory neuropathy, CIDP and MG and was twice as more frequent in those with inflammatory neuropathy than in other patients (25). Hypovolemia due to insufficient oral intake and semi-recumbent position may contribute to hypotension. Because it has been associated with intradialytic instability in hemodialysis patients (26) and frequently reported in CIDP (27, 28), autonomic dysfunction may also play a role in TPE-associated hypotension in CIDP patients.

Our observation of an association between hypotension and HES use was unexpected. The use of HES was recommended in France to improve haemodynamic tolerance of TPE (14, 29, 30). An allergic reaction due to HES without a cutaneous manifestation was unlikely (31). Because HES was infused at the beginning of the procedure, it is possible that rapid elimination of the HES volume (>75%) during TPE resulted in hypotension (32). However, other confounding factors could not be excluded. This finding led us to abandon the use of HES during TPE.

Our study estimated the incidence of hypocalcemia to be approximately 20%, despite calcium infusion during the TPE sessions, and it was more frequent with the use of FFP. This side effect was however largely asymptomatic (73% of cases). Our calcium replacement protocol contributed to the reduction of both the degree of hypocalcemia and associated symptoms. However, systematic calcium replacement is not a uniform practice among TPE centers.

FFP was strongly associated with allergic reactions, whereas A and HES were not. It is already known that allergic reactions are not rare during TPE, in particular in the treatment of thrombotic thrombocytopenic purpura (24, 33). The association between the volume of FFP infused and the risk of developing an allergic reaction was shown. This intuitive result underscores the need to curtail the volume of FFP required. Moreover, we observed a higher risk of allergic reaction when using quarantined-FFP than pathogen-inactivated FFP. This finding is in accordance with those already published by the International Hemovigilance Network (34). Whether pooled FFP should be used for large volume FFP TPE in order to reduce allergic reactions deserves further investigation.

Other manifestations, not associated with hypotension, hypocalcemia, or an allergic reaction, were frequently reported during the TPE sessions (malaise, digestive symptoms). They may have been due to ACD-A induced hypomagnesemia (unmonitored) or ACD-A toxicity alone.

Catheter-related complications were frequent, generally not serious and mostly associated with the use of a peripheral venous catheter. Our results suggest that the use of a dialysis catheter is reasonable when TPE sessions are frequent and large volumes are to be exchanged.

Our study had several strengths. First, the same standardized protocol was used for all TPE sessions, leading to the collection of data that was more homogenous than that of previously published studies (12, 13, 36). Second, the prospective recording of adverse effects during the

procedures by experienced nurses permitted the precise classification of adverse effects and not only a description of the symptoms (23). The reporting of adverse effects was therefore more exhaustive than that based on data from registries. It is likely that the 3 to 5% complication rates reported in these studies were considerable underestimates (12, 21, 35).

Our study also had a number of limitations, in particular its being a single center study and the retrospective nature of the work. Moreover, our monitoring form did not include surveillance of the corporeal temperature, whereas Shemin et al. (19) reported that fever occurred during 7.7% of TPE sessions. This could be helpful for the diagnosis of transfusion-related adverse events or for the better detection of infections. No other published study has reported fever during TPE sessions.

In conclusion, we report a high rate of adverse effects, mostly asymptomatic or mild. Serious adverse effects were rare. The main determinant of the complication rate was the replacement fluid. FFP was associated with the occurrence of allergic reactions and hypocalcemia. Hypotension was more frequent with the use of 4% A and was associated with the use of HES. Most catheter-related complications occurred with the use of a peripheral venous catheter.

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Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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FIGURE LEGENDS

Figure 1. Flow chart

TPE: therapeutic plasma exchange

TABLE 1. Indications for therapeutic plasma exchange sessions

Diagnosis	TPE sessions				Patients (N = 185)	Number of sessions per patient ^a
	All N = 1895	4% A N = 933	FFP N = 596	A + FFP N = 366		
TMA	488 (25.8%)				55 (29%)	
TTP	139 (7.3%)	0	139 (23.3%)	0	11 (6%)	10 [6-18]
non TTP TMA	349 (18.4%)	0	349 (58.6%)	0	44 (24%)	7 [4-11]
CNS disease ^b	148 (7.8%)	142 (15.2%)	0	6/366 (1.6%)	28 (16%)	5 [4-6]
ANCA-associated vasculitis	136 (7.2%)	36 (3.9%)	45 (7.6%)	55/366 (15.0%)	19 (10%)	7 [6.26]
Graft rejection	211 (11.1%)	61 (6.5%)	7 (1.2%)	143/366 (39.1%)	17 (9%)	9 [8-14]
Desensitization prior to transplantation	127 (6.7%)	35 (3.8%)	1 (0.2%)	91/366 (24.9%)	9 (5%)	15 [6-21]
CIDP	122 (6.4%)	120 (12.9%)	1 (0.2%)	1/366 (0.3%)	9 (5%)	6 [4-10]
Myasthenia gravis	144 (7.6%)	137 (14.7%)	0	7/366 (1.9%)	8 (4%)	5 [4-6]
Hyperviscosity syndrome	63 (3.3%)	51 (5.5%)	0	12/366 (3.3%)	7 (4%)	2 [2-2]
Cryoglobulinemia	44 (2.3%)	19 (2.0%)	3 (0.5%)	22/366 (6.0%)	7 (4%)	4 [4-6]
Acute liver failure	14 (0.7%)	0	14 (2.3%)	0	6 (3%)	3 [1-3]
Hemolytic anemia	19 (1.0%)	1 (0.1%)	2 (0.3%)	16/366 (4.4%)	5 (3%)	3 [1-7]
FSGS	306 (16.2%)	305 (32.7%)	0	1/366 (0.3%)	5 (3%)	27 [11-104]
Goodpasture disease/AH	51 (2.7%)	5 (0.5%)	34 (5.7%)	12/366 (3.3%)	5 (3%)	8 [6-12]
Neuro-lupus	9 (0.5%)	9 (1.0%)	0	0	2 (1%)	4.5 [4-5]
Other diagnosis ^c	13 (0.7%)	12 (1.3%)	1 (0.2%)	0	3 (2%)	2 [1-8]

Abbreviations: A, albumin; AH, alveolar hemorrhage; ANCA, anti-neutrophil cytoplasmic antibodies; CIDP, chronic inflammatory demyelinating polyneuropathy; CNS, central nervous system; FFP, fresh frozen plasma; FSGS, focal segmental glomerulosclerosis; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

^aValues are medians (25th percentile-75th percentile).

^bMultiple sclerosis, neuromyelitis optica (Devic's disease), encephalopathy, myelitis, acute disseminated encephalomyelitis.

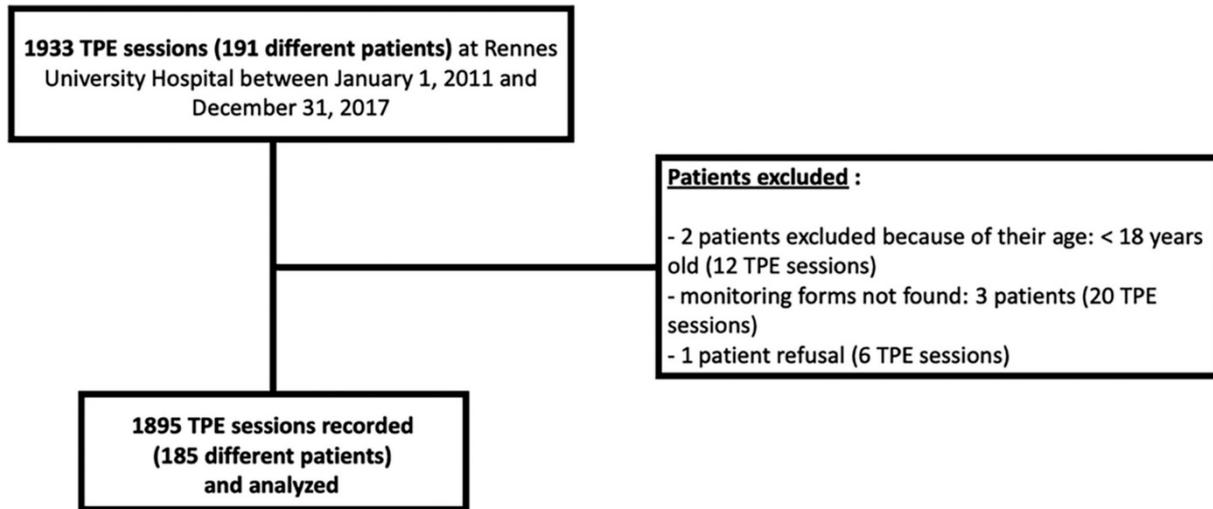
^cAlveolar proteinosis, thyroid storm, and phenylhydrazine intoxication.

TABLE 2 Characteristics of the 1895 therapeutic plasma exchange sessions

Variables	Total N = 1895	4%Albumin N = 933	Fresh frozen plasma N = 596	4% Albumin + fresh frozen plasma N = 366
<i>Duration (minutes)</i>	109 [97-123]	103 [93-114]	120 [105-138]	110 [99-121]
<i>Volumes, replacement fluids, anticoagulation and calcium substitution</i>				
Exchange volumes prescribed				
Total volume (mL)	4000 [3400-4600]	4000 [3250-4500]	4250 [3600-4900]	3750 [3250-4500]
Total volume (mL/kg)	55.9 [50-61.5]	52.3 [47.4-56.5]	60.9 [55.6-66.7]	56.3 [50.7-62.5]
Albumin volume (mL)		3250 [2500-3500]		2000 [1500-2500]
Fresh frozen plasma volume (mL)			4200 [3600-4900]	1600 [1300-2000]
Hydroxyethyl starch prescribed: yes-no. (percent)	848 (44.8)	750 (80.4)	1 (0.2)	97 (26.5)
Hydroxyethyl starch volume (mL)	500 [500-1500]	1000 [500-1500]	500	500 [500-500]
Total blood volume processed (mL)	7134 [6057-8186]	7630 [6275-8429]	6771 [5873-7794]	6749 [5846-7640]
Total blood volume effectively treated (mL)	6642 [5704-7536]	6981 [5757-7681]	6430 [5582-7419]	6366 [5600-7032]
Exchange volume effectively substituted (mL)	3918 [3354-4536]	3905 [3168-4449]	4197 [3551-4745]	3728 [3320-4352]
Albumin volume substituted (mL)		3250 [2500-3500]		2000 [1500-2500]
Fresh frozen plasma volume substituted (mL)			4119 [3566-4723]	1600 [1300-2000]
Ratio of exchanged volume to estimated plasma volume	1.3 [1.2-1.4]	1.3 [1.2-1.4]	1.4 [1.2-1.5]	1.3 [1.2-1.4]
Volume of ACD-A used during procedure (mL)	559 [476-663]	631 [527-709]	495 [432-556]	535 [472-608]
Volume of ACD-A reinfused (mL)	129 [75-439]	78 [63-106]	445 [378-518]	417 [350-478]
Total calcium administered during session (mmol)	10 [7-13]	9 [6.5-10]	12 [9-18]	11 [8-15]
<i>Hemodynamic characteristics</i>				
Baseline systolic arterial pressure (mm Hg)	135 [120-149]	137 [122-150]	134 [122-148]	128 [112-145]
Baseline diastolic arterial pressure (mm Hg)	71 [62-80]	71 [61-79]	74 [65-84]	68 [61-76]
Baseline mean arterial pressure (mm Hg)	93 [83-101]	93 [84-102]	95 [86-103]	89 [69-98]
Baseline heart rate (beats per minute)	83 [73-94]	80 [70-90]	86 [76-97]	88 [75-100]
Lowest mean arterial pressure during session (mm Hg)	82 [73-92]	81 [72-89]	87 [79-96]	79 [72-90]
Decrease in systolic arterial pressure from baseline (mm Hg)	9 [1-17]	11 [2-21]	6 [0-14]	8 [2-15]
<i>Biological characteristics</i>				
Ionized calcium before session (mmol/L)	1.16 [1.1-1.21]	1.18 [1.13-1.23]	1.14 [1.07-1.20]	1.14 [1.07-1.19]
Ionized calcium after session (mmol/L)	1.15 [1.07-1.22]	1.16 [1.1-1.22]	1.14 [1.04-1.22]	1.14 [1.07-1.23]
pH before session	7.39 [7.36-7.43]	7.38 [7.35-7.41]	7.41 [7.38-7.45]	7.39 [7.36-7.43]
pH after session	7.36 [7.3-7.43]	7.29 [7.25-7.33]	7.45 [7.41-7.48]	7.36 [7.32-7.40]
Hematocrit before session (%)	30 [37-36.5]	34 [30-40]	26 [24-29]	30 [26-33]
Hematocrit after session (%)	30 [27-36]	34 [30-39]	26 [24-29]	30 [26-33]
<i>Venous access—no. (percent)</i>				
Dialysis catheter (any site)	1027 (54.2%)	208 (22.3%)	512 (85.9%)	307 (83.9%)
Jugular	706 (68.7%)	156 (75%)	381 (74.4%)	169 (55%)
Femoral	255 (24.8%)	45 (21.6%)	124 (24.2%)	86 (28%)
Subclavian	61 (5.9%)	7 (3.4%)	7 (1.4%)	47 (15.3%)

TABLE 2 (Continued)

Variables	Total N = 1895	4%Albumin N = 933	Fresh frozen plasma N = 596	4% Albumin + fresh frozen plasma N = 366
Peripheral venous catheter	436 (23%)	358 (38.3%)	52 (8.7%)	26 (7.1%)
Arteriovenous fistula	278 (14.7%)	232 (24.9%)	23 (3.9%)	23 (6.3%)
Canaud catheter	146 (7.7%)	135 (14.5%)	4 (0.7%)	7 (1.9%)
Veno-venous extracorporeal membrane oxygenation device	8 (0.4%)	0	5 (0.8%)	3 (0.8%)



Flow chart. TPE, therapeutic plasma exchange

Supplementary material 1. Prescription and monitoring forms.



THERAPEUTIC PLAMA EXCHANGES PRESCRIPTION
UERTU UF6402

TPE nurse : 02 99 28 99 27 - Dr C. Camus: 85471
Fax ICU : 02 99 28 41 64
Fax FBS : 02 99 54 83 20 (16 601)

Étiquette Patient

Date:
Specialist physician:
Prescriber: Department:
Signature:

Prescription				
Indication:				
Session number / previous number of sessions: /			Frequency:	
Patient's characteristics				
Height:	Weight:	Haematocrit:		
Session's characteristics				
Volume to exchange	-----	mL		
Substitution fluid				
<input type="checkbox"/> Albumin 4%	-----	mL		
<input type="checkbox"/> Hydroxyethylstarch	-----	mL		
<input type="checkbox"/> Fresh frozen plasma.	-----	mL		
Calcium substitution				
<input type="checkbox"/> calcium gluconate:	g/h			
<input type="checkbox"/> calcium chloride:	g/h			
Blood test /Treatment				
.... h h h h h

Therapeutic plasma exchange: monitoring form

Nurse: Date: Weight: High:		Device number: Session number:		Haematocrit: Haemoglobin: Platelets:		Ionized calcium before: after:					
Treatment Fluid substitution <input type="checkbox"/> Albumin 4%: <input type="checkbox"/> FFP: <input type="checkbox"/> calcium gluconate: g/h <input type="checkbox"/> calcium chloride: g/h				Venous access <input type="checkbox"/> Dialysis catheter Insertion date: Localisation site: Aspect: <input type="checkbox"/> PVC: <input type="checkbox"/> AVF:							
Time	Blood pressure	Heart rate	Respiratory rate – SpO2	Blood debit	Plasma debit	Subst. fluid debit	ACD-A debit	Infusion Ratio	P*in P*out	Centri	Comments
Transmissions:										Kit number:	
Duration:				Plasma volume:			Next session:				
Blood volume treated:				Subst. fluid volume:			Substituion fluid to provide:				
Plasma ratio exchanged:				Calcium gluconate:			<input type="checkbox"/> Albumin 4%:				
Patient ACD-A infusion:				Calcium chloride:			<input type="checkbox"/> FFP:				

Supplementary material 2. Adverse event classification.

Hypotension

Once the diagnosis of hypotension was made, it was classified according to severity:

- grade I: asymptomatic hypotension if there were no associated symptoms and no specific therapy was given
- grade II: non-severe symptomatic hypotension if there was a need for volume expansion or increasing the dose of a vasoactive agent
- grade III: severe symptomatic hypotension if TPE session had to be stopped because of low blood pressure

Hypocalcemia

The severity of hypocalcemia was determined according to the Lee classification (17)

- grade I: asymptomatic (symptomless hypocalcemia)
- grade II: mild (perioral and/or distal paresthesia, sneezing, dizziness, flushes, chills, headache)
- grade III: moderate (nausea/vomiting, irritability, abdominal cramps, spasms, hypotension, tremor)
- grade IV: severe (heart rhythm disorders, attack)

Allergic reactions

The severity of allergic reactions was determined according to the Ring and Messmer classification (18):

- grade I: general skin signs (erythema, urticaria, edema)
- grade II: moderate multi-visceral disorders (skin/mucosal signs, hypotension or unusual tachycardia, bronchial hyperreactivity)
- grade III: life threatening multi-visceral disorders that required specific therapy (collapse, tachycardia or bradycardia, heart rhythm disorders, bronchospasm)
- grade IV: allergic reactions complicated by cardiac arrest

Supplementary material 3. Bacteriological documentation of catheter-related infections.

Catheter-related infection	Bacteriological documentation	Catheter site
<u>Catheter-related bacteremia</u> - catheter n°1 - catheter n°2 - catheter n°3 - catheter n°4 - catheter n°5	Methicillin-susceptible <i>Staphylococcus aureus</i> <i>Escherichia coli</i> (Extended spectrum beta-lactamase-producing) Methicillin-resistant <i>Staphylococcus epidermidis</i> <i>Pseudomonas aeruginosa</i> , wild-type phenotype Methicillin-resistant <i>Staphylococcus aureus</i> Methicillin- susceptible <i>Staphylococcus aureus</i>	jugular vein femoral vein jugular vein jugular vein jugular vein
<u>Colonization</u> - catheter n°6 - catheter n°7 - catheter n°8 - catheter n°9 - catheter n°10 - catheter n°11 - catheter n°12 - catheter n°13 - catheter n°14 - catheter n°15 - catheter n°16 - catheter n°17 - catheter n°18 - catheter n°19 - catheter n°20 - catheter n°21 - catheter n°22	Methicillin- susceptible <i>Staphylococcus epidermidis</i> Methicillin-resistant Coagulase-negative <i>Staphylococcus</i> Methicillin-resistant <i>Staphylococcus epidermidis</i> Methicillin-resistant <i>Staphylococcus epidermidis</i> Methicillin-resistant <i>Staphylococcus epidermidis</i> <i>Staphylococcus epidermidis</i> Methicillin-resistant <i>Staphylococcus epidermidis</i> <i>Staphylococcus epidermidis</i> Methicillin-resistant Coagulase-negative <i>Staphylococcus</i> Methicillin-resistant <i>Staphylococcus epidermidis</i> <i>Staphylococcus epidermidis</i> , <i>Pseudomonas aeruginosa</i> , wild-type phenotype Methicillin-susceptible <i>Staphylococcus epidermidis</i> <i>Staphylococcus capitis</i> Methicillin-resistant <i>Staphylococcus epidermidis</i> <i>Staphylococcus epidermidis</i> <i>Escherichia coli</i> (penicillinase-producing) Methicillin-resistant <i>Staphylococcus epidermidis</i>	jugular vein jugular vein subclavian vein jugular vein jugular vein jugular vein femoral vein jugular vein jugular vein jugular vein jugular vein jugular vein jugular vein jugular vein jugular vein jugular vein