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Adverse Events and Infectious Complications in the Critically Ill Treated by Plasma Exchange: A Five-Year Multicenter Cohort Study

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OBJECTIVES: The aim of this study was to determine, in critically ill patients treated with therapeutic plasma exchange (TPE), the incidence of adverse events as well as the incidence of secondary infections and its predictive factors.

DESIGN: A multicenter retrospective cohort study of an intensive care population treated with TPE to collect adverse events and infectious complications. The characteristics of patients who developed an infection after plasma exchange were compared with those of patients who did not.

SETTING: Four ICUs of French university hospitals.

PATIENTS: All adults admitted between January 1, 2015, and December 31, 2019, who received at least one plasma exchange session were included.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: A total of 711 TPE sessions were performed on 124 patients. The most frequent TPE indications were thrombotic microangiopathies ($n = 32$, 26%), myasthenia gravis ($n = 25$, 20%), and acute polyradiculoneuropathy ($n = 12$, 10%). Among the 124 patients, 22 (21%) developed arterial hypotension, 12 (12%) fever, and 9 (9%) electrolyte disturbance during TPE. Moreover, 60 (48%) presented at least one infectious complication: ventilator-associated pneumonia 42, pneumonia 13, bacteremia 18 (of which 6 catheter-related infections) viral reactivation 14. Independent risk factors for ICU-acquired infection were the ICU length of stay (24 vs. 7 d; hazard ratio [HR]: 1.09 [1.04–1.15], $p < 0.001$) and invasive mechanical ventilation (92% vs. 35%; HR: 16.2 [5.0–53.0], $p < 0.001$).

CONCLUSIONS: In critically ill patients treated with TPE, adverse events occurring during the procedure remain moderately frequent and are mostly not life-threatening. Infectious complications, mainly ventilation-associated pneumonia, are frequent in this population. The need of mechanical ventilation and longer ICU stay is associated with an increased risk of infection.

KEYWORDS: Adverse events; Infectious complication; Intensive care unit; Therapeutic plasma exchange

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique designed for the removal of high-molecular-weight substances including pathogenic antibodies and immune complexes (1). This treatment could induce adverse effects during the procedure. Major adverse event rates ranging from 0% to 3% and minor adverse event rates ranging from 8% to 30% have been previously reported (2–5). It may also predispose patients to the onset of secondary infections, probably because of the elimination of immunoglobulins and complement (6). Multiple treatments, especially when associated with immunosuppressive agents, will yield a substantial decrease in immunoglobulin levels that may persist for several weeks (1). This

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KEY POINTS

Question: What is the incidence of adverse events during therapeutic plasma exchange (TPE) in critically ill patients, and of infectious complications, and what risk factors are associated with them?

Findings: In this multicenter cohort study, the incidence of adverse events during TPE was moderate. A significant incidence of infectious complications after plasma exchange was observed in these critical care patients. These infectious complications were significantly associated with the need for mechanical ventilation (hazard ratio [HR]: 16.2 [5.0–53.0], $p < 0.001$) and longer ICU stay (HR: 1.09 [1.04–1.15], $p < 0.001$).

Meaning: Clinicians should be alert to the development of infectious complications in the critically ill treated with TPE.

induced infectious risk will be even higher in the critically ill treated by TPE. Indeed, TPE may be indicated in the critical care setting as primary or adjunctive therapy for hematologic, neurologic, renal, and autoimmune disorders (7).

Critically ill patients often develop multiple organ failure and require mechanical ventilation and central venous access. Several studies reported the ease, feasibility, and good tolerance of TPE therapy in ICU settings (2, 4). Most of the studies evaluated mainly the adverse effects occurring during the procedure (3, 8) but little is known about its impact on the occurrence of infections during and after the treatment. We therefore conducted this retrospective multicenter study in tertiary hospital ICUs to determine the incidence of TPE-related adverse events, as well as the secondary occurrence of infections and its predictive factors.

MATERIALS AND METHODS

This observational retrospective cohort study was carried out, from January 1, 2015, to December 31, 2019, in four French university hospital ICUs. The investigator for each site retrieved eligible patients by screening the term "plasma exchange" in ICU databases using the "Programme de Médicalisation des Systèmes d'Information". Each center collected data from the patient's computerized and/or paper medical records and reported it in a data sheet.

The Institutional Review Board of Montpellier University Hospital approved the study "Adverse events and complications associated with therapeutic plasma exchange in the intensive care unit: a five-year retrospective multicenter study" (approved date: September 16, 2021, number: 202100922) and waived the need of patient informed consent. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as most recently amended.

Population

All medical records of consecutive patients more than 18 years old who received at least one plasma exchange in ICU during the study period were reviewed. No exclusion criteria were applied, with the exception of pregnant women.

Data Collection

Demographic data and morbidities were collected. Characteristics and main treatment of underlying disease were collected including immunosuppressive therapy (azathioprine, rituximab, cyclophosphamide, mycophenolate mofetil), and corticosteroid (prednisone-equivalent daily dose ≥ 7.5 mg) within 1 month prior to ICU admission.

The severity of disease was assessed 24 hours after admission with the Simplified Acute Physiology Score II (SAPS II) and Sequential Organ Failure Assessment (SOFA) score (9, 10). Treatments administered during ICU stay were collected including invasive mechanical ventilation, high-flow nasal oxygen therapy, renal replacement therapy, vasopressor support, and their respective durations. Immunosuppressive treatments administered and associated with TPE during the ICU stay were also collected.

Plasma Exchange Therapy

TPE indication and the following TPE characteristics were collected: TPE modality (plasma filtration, double cascade filtration, or centrifugal method); total number of sessions, volume of plasma treated per session, substitution fluid, vascular access, and per-procedure anticoagulation.

Any procedural and patient complications occurring during TPE were collected. The following per-procedure adverse events were retrieved: pruritus or urticaria, nausea or vomiting, fever defined as a temperature greater than or equal to 38°C or chills, hypotension defined as a fall in systolic blood pressure greater than or equal to 20% or a systolic blood pressure less than or equal to 90 mm Hg, arrhythmia and electrolyte disorder requiring medical intervention, cardiac arrest, and convulsion.

Our key aim was to collect ICU-acquired infectious after TPE therapy onset. These events were considered associated with TPE when they occurred de novo and 2 days or more after the start of treatment. They included pneumonia, ventilator-associated pneumonia (VAP), bacteremia, catheter-associated infection (CAI), and viral reactivation.

Diagnosis of pneumonia was retained (11), if there was an evocative image (on ultrasound, radiography, or CT scan) associated with at least one of the following signs: fever higher than 38°C without any other cause, leukocytes less than 4 G/L or more than 12 G/L and at least one of the following signs: appearance of purulent secretions or change in secretions (odor, color, quantity, consistency), cough or dyspnea or tachypnea, suggestive auscultation, or blood gas desaturation or increased oxygen or ventilatory support requirements.

A diagnosis of VAP was retained if the criteria for pneumonia were met more than 48 hours after invasive mechanical ventilation onset.

Bacteremia was defined as the presence of a blood culture-identified bacterium in the circulating blood. For commensal organisms (coagulase-negative *Staphylococcus*, *Cutibacterium* species, *Bacillus* species, *Micrococcus* species, *Corynebacterium* species), two blood cultures were required to secure the diagnosis. Identification of a fungus on blood cultures was reported as fungemia.

A diagnosis of CAI was retained (12) when there was a positive culture ($\geq 10^3$ colony-forming units/mL) of the removed catheter and a total or partial regression of the infectious signs within 48 hours of catheter removal, or catheter tunnelitis or catheter port purulence. In the case of bacteremic CAI, the infectious event was reported as CAI. Viral reactivation was considered if epstein Barr virus, Cytomegalovirus, or herpes simplex virus replication was found by polymerase chain reaction in the blood.

Septic shock was defined (13) by the association of sepsis, a need for vasopressor drugs to obtain a mean arterial pressure greater than or equal to 65 mm Hg and a lactatemia greater than or equal to 2mmol/L after fluid resuscitation.

Outcome

Lengths of stay in ICU and mortalities in ICU and hospital were collected. Death by limitation of care, including continued mechanical ventilation, possible renal replacement therapy, and prolonged administration of vasoconstrictor amines, was recorded.

Statistical Analysis

The main objective of the study was to determine the incidence of adverse events and the incidence of infectious events following TPE. This incidence of nosocomial infections was compared with that of matched critically ill control patients with the same comorbidities (including hypertension, diabetes mellitus, NYHA ≥3 stage heart failure, and ischemic heart disease), severity, and duration of mechanical ventilation who did not undergo TPE. A power analysis was used to determine the appropriate sample size for matching using the epiR package 0.9-96 (version 0.9-96, Stevenson, Australia). Knowing that the rate of ICU-acquired infection is about 30% in the literature and 48% in our cohort, we determined the sample size for detecting a 20% difference between two groups with a significance level (α) of 0.05 and a power ($1 - \beta$) of 90% and found that 101 patients per group were required. Thus, we performed a 1:1 matching (124 in each group), considering 2:1 or 3:1 matching to ensure balance was not mandatory.

We sought also to identify the factors associated with the observed infectious events following TPE.

Categorical data were described as numbers and percentages, and continuous data as medians with 25th and 75th percentiles (IQR). Categorical variables were compared by chi-square or Fisher exact test, and continuous variables were compared by Student *t* test or Wilcoxon rank-sum test as appropriate.

A Kaplan-Meier survival curve was performed to compare TEP patients who experienced at least one infectious event and those who did not, using the log-rank test. Then, the incidence of infectious events following

TPE was compared with that of matched critically ill control patients on comorbidities, severity, and duration of mechanical ventilation who did not underwent TPE therapy.

Factors associated with infectious events were assessed using univariable and multivariable cox regression model. A conditional stepwise regression with 0.1 as the critical *p* value in the univariate analysis for entry into the multivariate analysis was performed to select the most informative variables. In the case of interactions and correlations between the explanatory variables, only the most clinically relevant were included in the final model. Results of Cox regression model were reported as hazard ratio (HR) with 95% CI.

All tests were two-sided and a *p* value less than 0.05 was considered statistically significant. R software version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org/) was used for analyses.

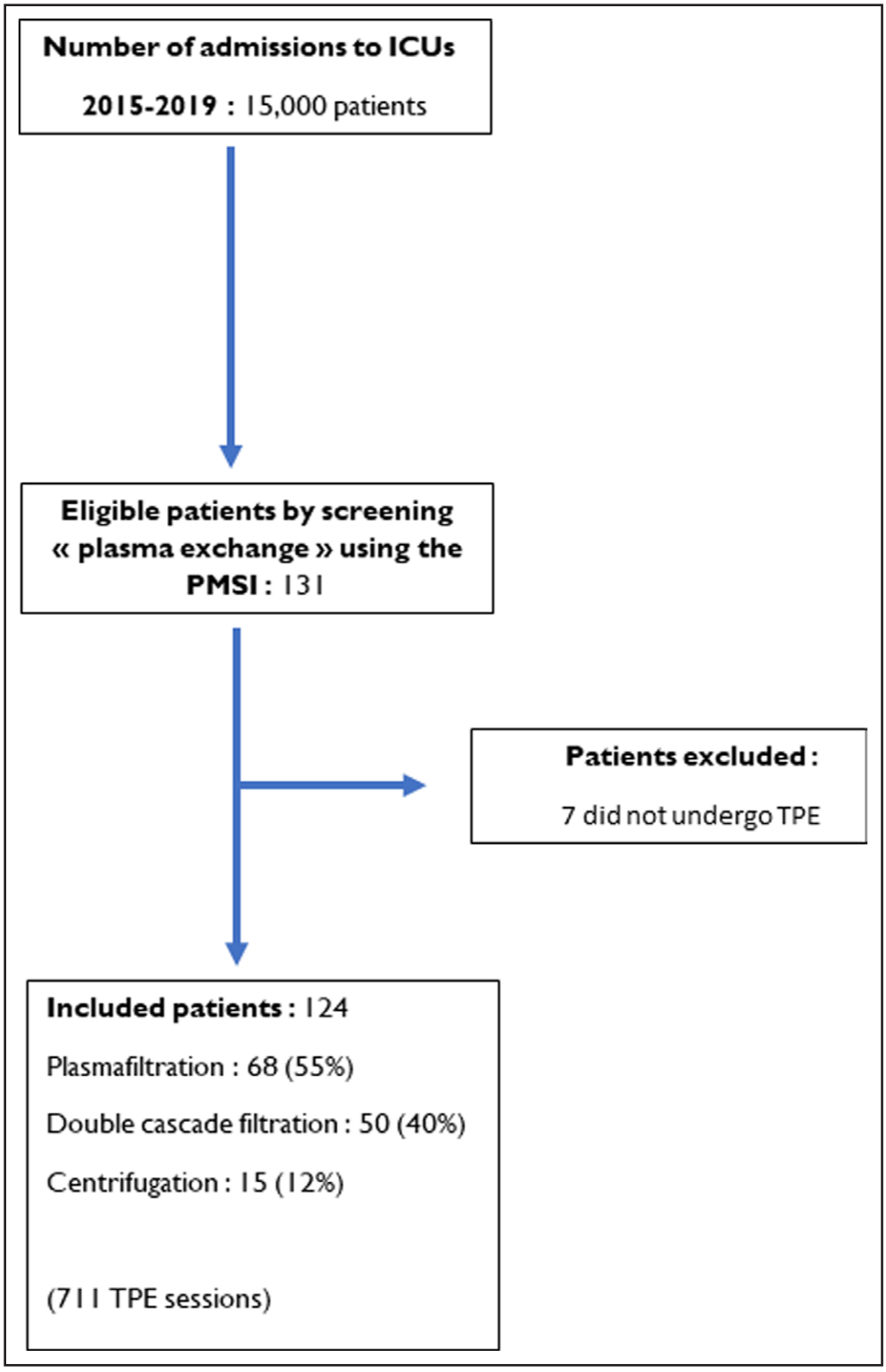

Figure 1. Flow chart of the studied population (several techniques can be used in the same patient's treatment program). PMSI = Programme de Médicalisation des Systèmes d'Information, TPE = therapeutic plasma exchange.

RESULTS

Population

One hundred twenty-four patients (69 women, 56%) with a median age of 54 years were included in the study (**Fig. 1**). The patients' characteristics are displayed in **Table 1**. As shown in Table 1, high SAPS II and SOFA scores at ICU admission underlined the severity of the patient illnesses. During ICU stay, 78 patients (63%) required mechanical ventilation for a median time duration of 14 days. Also, 56 (45%) patients received vasoactive drugs for a median time of

TABLE 1.
Characteristics of the Population, Severity Scores, Management, and Outcome During ICU Stay

Characteristics: *N* (%) or Median [Q1–Q3]	Patients (*n* = 124)
Admission	
Age, yr	54 [39–67]
Male gender	55 (44)
Weight, kg	68 [60–80]
Previous immunosuppressive treatment	
Corticosteroid therapy	28 (23)
Others[a]	36 (29)
ICU stay	
Sequential Organ Failure Assessment	5 [2–8]
Simplified Acute Physiology Score II	36 [25–51]
Noninvasive ventilation	22 (18)
Duration, d	3 [2–6]
High-flow oxygen therapy	13 (10)
Duration, d	3 [1–5]
Invasive mechanical ventilation	78 (63)
Duration, d	14 [7–22]
Renal replacement therapy	36 (29)
Duration, d	10 [3–17]
Vasopressor support	56 (45)
Duration, d	6 [2–11]
Immunosuppressive treatment	
Corticosteroid therapy, bolus	44 (35)
Corticosteroid therapy, ≥1 mg/kg/d	77 (62)
Rituximab	28 (23)
Cyclophosphamide	11 (9)
Eculizumab	9 (7)
Length of stay, d	
ICU	14 [7–26]
Hospital	39 [21–63]
Mortality	
ICU	18 (14)
Hospital	27 (22)

[a]Rituximab, cyclophosphamide, mycophenolate mofetil, and azathioprine.

6 days. Thirty-six patients (29%) underwent renal replacement therapy that lasted for 10 days. More than 25% of patients had received immunosuppressive treatment prior to ICU admission (Table 1).

Plasma Exchange Therapy and Per-Procedure Adverse Events

During the study period, 711 plasma exchange sessions were completed. The main indications for TPE were thrombotic microangiopathy (26%), acute myasthenia gravis (20%), and acute polyradiculoneuritis (10%). The plasma exchange technique was mainly plasma filtration (55% of patients) or double cascade filtration (40%), as different techniques can be used in the same patient during the treatment course. Vascular access was internal jugular site in more than half of the population (56%). Regional citrate anticoagulation was frequently used, in almost two thirds of patients (61%). A number of five sessions (2–7), with a median plasma volume at 52 mL/kg/session, was carried out per patient for a median duration of 7 days (3–12). Replacement fluid was fresh–frozen plasma (43%), 20% albumin (37%), or both (28%). Additional data about TPE are summarized in **Table 2**.

As shown in Table 2, adverse events that occurred during the procedure were mainly arterial hypotension (22 patients, 21%) and fever (12 patients, 12%). During TPE, a hemorrhagic event requiring medical intervention was reported in 18 (15%) patients and 16 (13%) patients experienced acute pulmonary edema which quickly resolved.

Infectious Complications After the Start of TPE

The median time to onset of the first infectious complication was 9 days after ICU admission and 5 days after the first TPE session. Almost half of patients (48%) experienced at least one infectious event during the period of treatment. Of these patients, almost all developed pneumonia, including 42 VAPs (Table 2). Septic shock occurred in about one third (31%) of infected patients.

The comparison to a control group that included 124 patients, not treated by TPE, similar in age, comorbidities, SOFA score, duration of mechanical ventilation, and ICU length of stay showed that the occurrence of infectious complications was significantly higher in the plasma exchange group (29 vs. 48%, $p = 0.002$) (**Table 3**).

To identify predictive factors of infectious risk following TPE therapy, we compared the studied patients with and without infection (**Table 4**). By univariate analysis, longer duration of plasma exchange therapy and renal replacement therapy, use of vasopressor

TABLE 2.
Indication, Adverse Events, and Infectious Complications After Therapeutic Plasma Exchange

N (%) or Median [Q1–Q3]	Patients (*n* = 124)
Indication for TPE	
Thrombotic microangiopathy	32 (26)
Myasthenia	25 (20)
Acute polyradiculoneuritis	12 (10)
Catastrophic antiphospholipid syndrome	9 (7)
ANCA vasculitis	8 (6)
Other	38 (31)
TPE modality and characteristics (711 sessions)	
Plasma filtration	68 (55)
Double cascade filtration	50 (40)
Centrifugation	15 (12)
No. of sessions per patient	5 [2–7]
Duration of treatment, d	7 [3–12]
Volume of plasma treated, mL/kg	52 [45–60]
Substitute products	
Plasma alone	53 (43)
Albumin alone	46 (37)
Plasma + albumin	35 (28)
Adverse events during TPE	
Arterial hypotension	22 (21)
Fever	12 (12)
Electrolyte disturbance	9 (9)
Arrhythmia	7 (7)
Pruritus-urticaria	3 (3)
Nausea-vomiting	2 (2)
Cardiac arrest	1 (1)
Infectious complications	
At least one infectious event	60 (48)
Pneumonia	55 (44)
Nosocomial pneumonia	13 (10)
Ventilator-associated pneumonia	42 (34)
Viral reactivation	14 (11)
Bacteremia	18 (14)
Catheter-related infection	6 (5)
Elapsed time to first infectious complication, d	
From ICU admission	9 [4–14]
From TPE initiation	5 [2–8]

TPE = therapeutic plasma exchange.

support, and use and longer duration of mechanical ventilation were significantly associated with higher occurrence of infectious complications, whereas thrombotic microangiopathy was associated with fewer infectious complications. However, only the need for mechanical ventilation and longer duration of ICU length of stay were independently associated with infectious complications by multivariate analysis (16.2 [5.0–53.0], $p < 0.001$ and 1.09 [1.04–1.15], $p < 0.001$; respectively).

Outcome

The median length of stay in the ICU was 14 days, and ICU and in-hospital mortality were 14% and 22%, respectively, similar to the control group. **Figure 2** displays the Kaplan-Meier curve of survival in infected and noninfected patients showing no significant differences.

DISCUSSION

In this study involving critically ill patients, adverse events during TPE were moderately frequent and mostly not life-threatening. Also, we found a relatively high incidence of infectious episodes following TPE. Almost half of our patients experienced at least one infectious complication in a median time of 5 days after the start of TPE. It was mainly a respiratory infection, especially pneumonia associated with mechanical ventilation. The need for invasive mechanical ventilation and a longer ICU stay were independent infectious risk factors. However, the occurrence of an infection does not significantly change the outcome of our patients.

Although plasma exchange is sparsely implemented in ICU settings, it is not an uncommon treatment modality. Several studies have looked at the per-procedure side effects of this treatment and reported a rate of major adverse events ranging from 0% to 3% and a rate of minor adverse events ranging from 8% to 30% (2, 4). TPE is then considered a safe and well tolerated therapy for the critically ill. Although 21% of our patients suffered arterial hypotension and 12% fever during the procedure, these events were mostly mild and resolved and were not life-threatening apart from one cardiac arrest.

Data about the infectious risk associated with TPE treatment are sparse, but this potential risk should not be ignored. Indeed, plasma exchange decreases the

TABLE 3.
Comparison of the Studied Population to the Control Group

N (%) or Median [Q1–Q3]	Control Group (*n* = 124)	Therapeutic Plasma Exchange Group (*n* = 124)	*p*
Age, yr	56 [41–68]	54 [39–72]	0.76
Gender (male)	73	55	0.22
Sequential Organ Failure Assessment	6 [3–9]	5 [2–8]	0.50
Simplified Acute Physiology Score II	43 [31–60]	36 [25–51]	0.01
Invasive mechanical ventilation	80 (64)	78 (63%)	0.79
Duration, d	13 [6–20]	14 [7–22]	0.75
Renal replacement therapy	25 (20)	36 (29)	0.11
Duration, d	4 [1–7]	10 [3–17]	0.06
Vasopressor support	78 (63)	56 (45)	0.01
Duration, d	4 [3–10]	6 [2–11]	0.79
ICU Length of stay, d	14 [6–24]	14 [6–26]	0.74
Mortality			
ICU	19 (15)	18 (14)	0.86
In-hospital	22 (18)	27 (22)	0.35
Withdrawal of life-sustaining treatments	26 (21)	20 (16)	0.33
Infectious events			
At least one infectious event	36 (29)	60 (48)	0.01
Ventilator-associated pneumonia	27 (22)	42 (34)	0.03
Pneumonia	4 (3)	13 (10)	0.24
Catheter-related infection	9 (7)	6 (4)	0.28
Blood stream infection	7 (5)	12 (9)	0.91
Septic shock	8 (6)	19 (15)	0.03
Viral reactivation	8 (6)	14 (11)	0.06

level of circulating immunoglobulins and complement proteins that might potentiate the risk of infection. In addition, most patients who are treated by this therapy may receive a concomitant immunosuppressive drug regimen. A quarter of our patients have received immunosuppressive drugs before ICU admission, and almost all of them received such during plasma exchange treatment. Also, critically ill patients are frequently mechanically ventilated, treated by vasoconstrictive agents, and may require renal replacement therapy requiring central vascular access. Thus, in our population, two thirds of them were on mechanical ventilation, 30% were treated by renal replacement therapy, and all had a central venous catheter and/or vascular access for plasma exchange therapy. All these factors may predispose patients to an increased incidence of infection. In such patients, the development of infectious complications following plasma exchange is of particular concern. Our data showed that almost half of our patients (48%) experienced a nosocomial infection after TPE. much higher than what we observe in ICU patients with similar severity and organ failure. For example, in the SOAP study (14), a large international cohort of ICU patients, at least one infectious complication was reported in 37.4% of patients knowing that 24.7% of whom were already septic at admission. Furthermore, in a more recent study carried out on a given day in several ICUs worldwide, the prevalence of proven or probable infection was 54%, but it was only 22% for ICU-acquired infection (15). To secure our hypothesis, we compared our study group with a matched ICU group that had similar age, comorbidities, severity, similar duration of mechanical ventilation, and even higher SAPS II score. The

TABLE 4.
Comparison of Infected and Noninfected Patients by Univariate and Multivariate Analysis

N (%) or Median [Q1–Q3]	Noninfected (*n* = 63)	Infected (*n* = 61)	Univariate Analysis, *p*	Multivariate Analysis, Hazard Ratio (95%), *p*
Age, yr	52 [36–65]	57 [48–69]	0.13	
Gender (male), *n* [%]	27 [44]	28 [46]	0.73	
Previous use of				
MP	14 (22)	14 (23)	0.92	
Other immunosuppressive therapy	16 (25)	20 (33)	0.40	
Indication for TPE				
Thrombotic microangiopathy	24 (34)	8 (13)	0.001	
Myasthenia	9 (14)	16 (26)	0.10	
Acute polyradiculoneuritis	4 (6)	8 (13)	0.21	
TPE characteristics				
No. of sessions per patient	3 [2–6]	6 [3–10]	0.14	
Duration, d	5 [2-8]	10 [5-15]	0.001	
Management in ICU				
Sequential Organ Failure Assessment	5 [2–8]	4 [2–8]	0.76	
Simplified Acute Physiology Score II	32 [19–44]	38 [28–54]	0.04	
Invasive mechanical ventilation	22 (35)	56 (92)	<0.001	16.2 [5.0–53.0], $p < 0.001$
Duration, d	6 [3–9]	17 [10–28]	0.001	
Renal replacement therapy	15 (24)	21 (34)	0.31	
Duration, d	4 [2–8]	15 [10–20]	0.002	
Vasopressor support	17 (27)	39 (64)	<0.001	
Duration, d	3 [2–6]	7 [3-14]	0.012	
Immunosuppressive therapy				
MP bolus	25 (40)	19 (31)	0.32	
MP ≥ 1 mg/kg/j	40 (64)	37 (61)	0.75	
Rituximab	15 (24)	13 (21)	0.74	
Cyclophosphamide	6 (10)	5 (8)	0.80	
Eculizumab	5 (8)	4 (7)	0.77	
Length of stay, d				
ICU	7 [4–14]	24 [17–37]	<0.001	1.09 [1.04–1.15], $p < 0.001$
Hospital	24 [12–49]	57 [33–75]	0.006	
Mortality				
ICU	6 (10)	12 (20)	0.11	
Hospital	12 (19)	15 (24)	0.50	
Withdrawal of life-sustaining treatments	6 (10)	14 (23)	0.042	

MP = methylprednisolone, TPE = therapeutic plasma exchange.

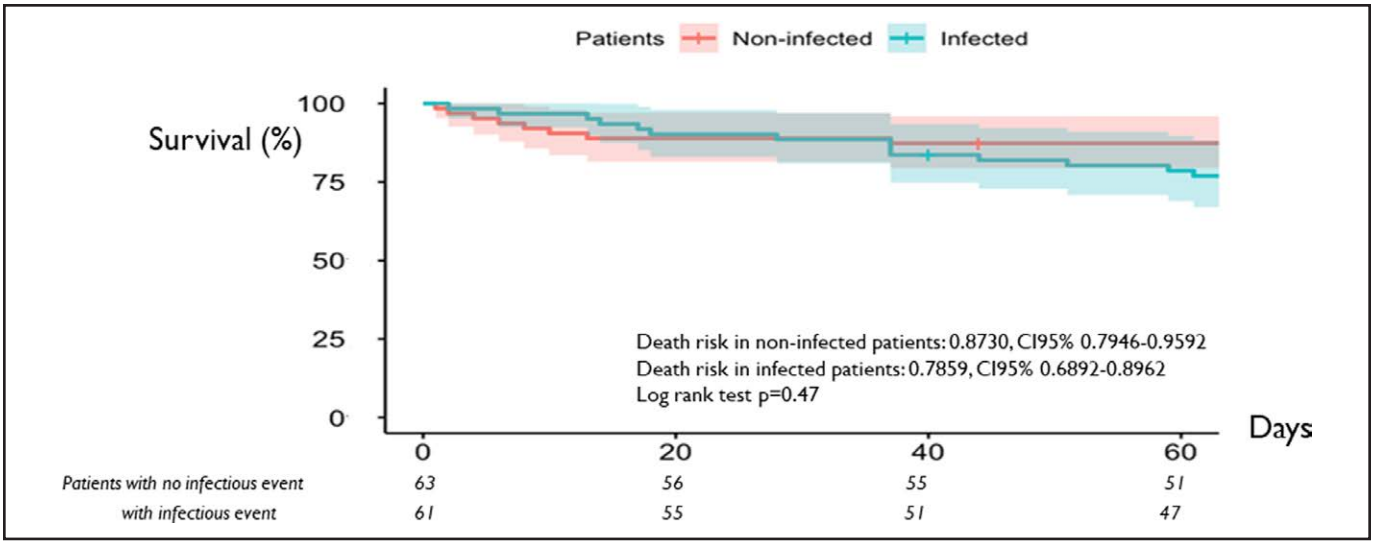

Figure 2. Actuarial survival of infected and noninfected patients treated by therapeutic plasma exchange during the ICU stay.

incidence of infectious complications was higher in the critically ill treated by plasma exchange, stressing the pejorative role of this therapeutic. However, we must recognize that our ICU control group does not necessarily have the same immunosuppression status as our study population.

Few data exist about infections in critically ill treated by TPE. Lemaire et al (4) found, in a retrospective study of 50 ICU patients treated by TPE, an infectious complication in only 12% of patients. However, in this report, patients' acuity was lower than in our population as reflected by severity scores (SAPS II 25 vs. 35), and a lower proportion requiring invasive mechanical ventilation (22% vs. 63%). Infections were mainly of respiratory origin and then bacteremia and catheter-related infections, similar to our findings. It is noteworthy that one third of our patients developed a septic shock which is a life-threatening condition.

Whether TPE is associated with infectious risk remains questioned. Our study cannot clearly answer this question, but it suggests an increased risk induced by this treatment owing to that no randomized study comparing patients treated or not with TPE has been reported. To the best of our knowledge, only four studies tried to assess this issue, all conducted in non-ICU patients. In the Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis controlled trial (16) randomized controlled trial that included 704 patients with ANCA vasculitis, the occurrence of an infectious complication was not different between TPE and non-TPE groups (39% vs. 32%; 1.19, 0.98–1.46). Pohl et al (17), by studying 86 patients with severe lupus nephritis (SLE) treated by immunosuppressive agents where half of them received TPE, found that this treatment did not increase the risk of infections, whereas Aringer et al (18) observed that severe infections were significantly more common in SLE patients undergoing TPE. As for Wing et al (19), the treatment by TPE led to life-threatening infections in five of eight patients with rapidly progressive glomerulonephritis compared with two of 21 not treated by TPE. They concluded that serious infections including opportunistic ones occur in one third of patients undergoing TPE for renal diseases. It is clear that our results do not allow us to establish a causal link between the occurrence of nosocomial infections and treatment with plasma exchange. However, we did observe a higher rate of secondary infections than is usually the case in ICUs.

Our concern was also to identify predictive factors of infection in our population. We found that the need for mechanical ventilation and prolonged length of ICU were independently associated with more infectious events. These factors are well recognized as risk factors in ICU patients (20). TPE poses an additional risk, especially when treatment is prolonged. Of note, the immunosuppressive drug regimen before or during the ICU stay did not influence the occurrence of infectious complications. Also, the site of vascular access, namely femoral site, was not associated with an increased infectious as reported previously (21, 22).

Finally, the outcome of our patients was satisfactory, with intensive care and hospital mortality of 14% and 22%, respectively. One striking thing was that

the occurrence of an infectious complication did not worsen significantly the prognosis.

Our study has both strengths and limitations. The strengths were that we had a large database of tertiary care units. Also, our study is the first multicenter study conducted in a large group of critically ill patients to report infectious complications following plasma exchange treatment. In addition, our population was compared with a control group with similar comorbidities, severity, length of ICU stay, and duration of mechanical ventilation. All patients were followed and outcomes were collected and reported comprehensively. The limitations are that it is a retrospective observational study with the biases that are inherent to such studies. The multicenter nature of the study may have contributed to heterogeneity in practices and data collection. We were unable to compare our study population with a control group not treated with TPE, with similar pathologies and a comparable degree of immunosuppression. Nevertheless, multivariate analysis did not show any association between the type of pathology and immunosuppressive treatment and the occurrence of an infectious complication. Moreover, infectious events that could occur after discharge from the ICU were not collected and investigated in this study.

CONCLUSIONS

Intraprocedural adverse effects of TPE, mainly arterial hypotension and fever, can occur in severely ill patients, but in most cases do not lead to serious complications. Infectious complications following TPE are common in these patients, mainly ventilation-associated pneumonia. The need for mechanical ventilation and an increased duration of length of stay in ICU are associated with an increased risk of infection. Although no mortality risk has been observed, TPE should be applied judiciously like any other invasive therapy in critically ill patients. The association of this infectious risk with TPE remains, however, to be assessed by further prospective controlled studies.

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Drs. Larcher, Daubin, and Klouche conceived the study. Drs. François, Daubin, Gaillet, Provoost, Trusson, Arrestier, Hequet, Richard, Moranne, Larcher, and Klouche collected data. Drs. Larcher, Klouche, Daubin, and François analyzed data. MF and RL provided graphical support. Drs. François, Daubin, and Klouche drafted the manuscript. All authors contributed to the revision and approved the final version of the manuscript.

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According to French law, written informed consent was not required for a retrospective study based on anonymous data extraction from patients' medical files and related analysis.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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