Treatment of Adults with Clinically Suspected Severe Thrombotic Thrombocytopenic Purpura – Experiences of a Single Centre

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Key Words

Plasma exchange · Immunotolerance · TTP

Summary

Background: Thrombotic thrombocytopenic purpura (TTP), even though uncommon, has an increasing prevalence and is fatal if untreated. Plasma exchange (PE), if started within 48 h of presentation, has improved the clinical outcome and reduced the mortality rate to 10–35%. Major complications and allergic reactions related to PE are reported to occur in about 50% of patients and catheter-related complications in up to 30% of patients. To further reduce mortality and relapses in patients with TTP, therapeutic strategies should aim at minimizing complications related to treatment. **Patients and Methods:** A total of 31 patients with clinically suspected severe TTP were treated with the following protocol: i) pre-medication with steroids and antihistamines just before each PE procedure; ii) continuous calcium gluconate substitution; iii) insertion of a jugular central venous catheter using the Seldinger technique under ultrasonic guidance; iv) continuous low-dose anti-coagulation treatment via the central venous catheter. **Results:** No treatment-related mortality occurred. In 434 PE procedures, none of our patients developed allergic reactions or major complications. The incidence of minor complications was less than 10%. Our insertion technique has a low complication rate of 14%. The centrifugal plasma separation technique prevents thrombocyte losses. Over an median follow-up of 3.5 years, the relapse rate amounted to 3%. **Conclusion:** Our protocol presented here allows a safe treatment of severe TTP with a low incidence of complications and a low relapse rate.

Schlüsselwörter

Plasmaaustausch · Immuntoleranz · TTP

Zusammenfassung

Hintergrund: Die thrombotisch-thrombozytopenische Purpura (TTP) ist eine seltene Erkrankung, die unbehandelt eine hohe Mortalität besitzt. Obwohl eine innerhalb der ersten 48 h nach Patientenvorstellung durchgeführte Plasmaaustausch(PE)-Therapie die Letalitätsrate deutlich senken konnte, versterben immerhin noch 10–35% der Patienten. Die Komplikationsrate der PE wird mit bis zu 50% angegeben, katheterassoziierten Komplikationen kommen bei bis zu 30% der Patienten vor, und die Rückfallrate liegt bei bis zu 11%. Ziel einer verbesserten Therapiestrategie zur weiteren Reduktion der Mortalität und zur Verhinderung von Rückfällen sollte daher sein, die Komplikationsraten der lebenswichtigen therapeutischen Maßnahmen zu minimieren. **Patienten und Methoden:** 31 Patienten mit klinisch vermuteter schwerer TTP wurden einheitlich mit dem folgenden Protokoll therapiert: 1) Prämedikation mit Steroiden und Antihistaminika; 2) kontinuierliche intravenöse Kalzium-Substitution; 3) ultraschallgesteuerte Anlage eines zentralvenösen jugulären Katheters mittels Seldinger-Technik; 4) kontinuierliche niedrig dosierte Heparinisierung des zentral venösen Katheters. **Ergebnisse:** In unserem Kollektiv traten keine therapieassoziierten Todesfälle auf. Auch allergische Reaktionen oder größere Komplikationen traten in den 434 durchgeführten PE-Therapien nicht auf. Die Rate leichterer Komplikationen lag bei unter 10% und die katheterassoziierte Komplikationsrate bei 14%. Bei der zentrifugalen Plasmaseparationstechnik traten keine separationsbedingten Thrombozytenverluste auf. Die Rückfallrate lag in einem medianen Beobachtungszeitraum von 3,5 Jahren bei 3%. **Schlussfolgerung:** Das vorgestellte Behandlungsprotokoll führt zu geringen Behandlungskomplikationen und stellt somit einen sinnvollen Therapiefahrplan besonders für schwere Fälle der TTP dar.

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening disease with an increasing incidence of approximately 3.7 per million persons per year [1, 2]. Plasma exchange (PE) treatment of TTP has reduced the mortality rate of TTP from 90 to 10–35% [3, 4]. Before the availability of PE, the diagnosis was based on the clinical observation of the following pentad of symptoms: thrombocytopenia, microangiopathic haemolytic anaemia, neurological symptoms (headache, coma, confusion, seizure, apoplexy), renal dysfunction and fever [5]. Today, the combination of microangiopathic haemolytic anaemia and unexplained thrombocytopenia is considered to be a sufficient criterion to suspect TTP and to initiate plasmapheresis [5–8]. An early start of PE is essential since the majority of deaths from TTP occur within 48 h of presentation [9].

Clinical overlaps of TTP and haemolytic uraemic syndrome (HUS) can occur and [6], indeed, acute renal failure, the clinical feature that is used to define HUS, may be present in TTP in about 5% of cases [6]. Consumption thrombocytopenia and microangiopathic haemolytic anaemia represent the main symptoms of both diseases, and the presence of neurological or renal symptoms is not regarded as a sufficient discriminatory criterion to distinguish between TTP and HUS. Therefore, some authors propose the use of thrombotic microangiopathy (TMA) as a unifying term, with HUS and TTP representing two clinical manifestations of TMA [10]. Furthermore, in adults with non-enterotoxin-related HUS (atypical HUS), the distinction between HUS and TTP is not regarded as important for the initial decision to start PE [6, 11].

Using both the clinical and the biological criteria, about 90% of patients with TTP exhibit a severe functional deficiency (<5%) of von Willebrand factor (vWF) cleaving proteases (ADAMTS13) during the acute phase of the syndrome [6]. ADAMTS13 is a disintegrin and metalloprotease with thrombospondin motifs that prevents inappropriate microvascular platelet aggregation by cleaving vWF between Tyr1605 and Met16006 [12]. Severe ADAMTS13 deficiency, acquired or inherited, leads to hyper-adhesive, ultra-large multimers of vWF (ULvWF) and appears to be a major specific risk factor for TTP [6]. However, this observation does not allow TTP to be redefined by an undetectable ADAMTS13 activity in plasma since other mechanisms cannot be excluded from participation in the diagnosis of TTP [6].

In adults, PE is the only treatment which is proven to be effective in therapy of TTP [2]. Studies on complications and incompatibilities of PE, especially in TTP patients, are rare [13, 14]. The PE procedure itself and the catheter implantation that is often necessary have been reported to be associated with a complication rate of up to 30% and a mortality rate of 10%. Additional minor complications are seen in about 31% of patients, resulting in an overall complication rate of 61% [13–15]. On the basis of recommendations by Rizvi et al. [13]

and our own experience in the treatment of coagulation disorders [16–18], we started from 2000 onwards to treat our TTP patients uniformly with the following protocol: i) treatment with steroids and antihistamines just before each PE procedure to protect the patient from allergic reactions; ii) continuous calcium gluconate substitution via a venous blood line to protect the patient from citric toxicity; iii) insertion of a jugular central venous catheter using the Seldinger technique under ultrasonic guidance; iv) continuous low-dose anticoagulation treatment via the central venous catheter to prevent catheter occlusions. This protocol was designed to effectively treat TTP with a minimum of side-effects.

Here, we present a retrospective analysis of 31 cases of TTP treated in our centre. The clinical data of the patients and the PE protocols of 434 procedures were analysed for treatment-related side-effects, safety and efficacy. The outcome and follow-up of all patients were documented over a median period of 3.5 years.

Patients and Methods

We analysed data of 31 adult patients with a clinically suspected diagnosis of TTP who were admitted to the Intensive Care Unit (ICU) of the Medical Policlinic of the University of Bonn between January 2000 and January 2005. Diagnostic criteria were as follows: i) microangiopathic haemolytic anaemia (haemoglobin level < 7 g/dl) and antiglobulin test negative; ii) three or more fragmented red cells or helmet cells per high-power field in the peripheral blood smear; iii) thrombocytopenia (platelet count < $75 \times 10^6/\mu\text{l}$) or a 50% drop compared with previous count. Neurological symptoms, renal function abnormalities or fever were not considered as diagnostic inclusion or exclusion criteria.

Each participating patient or the legal guardian (in the case of neurological symptoms on admission) gave written informed consent. The PE procedures were performed daily; the plasma volume of each patient was exchanged at least once.

On admission, all patients were screened for disorders associated with TTP (table 1), e.g. stem cell transplantation, gastrointestinal infections, respiratory infections, malignancy, autoimmune disease, HIV infection, pregnancy and medical treatment. All patients underwent tests for HIV, hepatitis A, hepatitis B and hepatitis C before PE. Patient laboratory data for haemoglobin, LDH, haptoglobin, liver and renal parameters were documented on admission and during PE therapy. The PE protocols of each procedure were analysed for major and minor complications associated with the PE procedure and the catheter insertion. Patients' vegetative functions, i.e. blood pressure, heart rate, heart rhythm, arterial pO_2 saturation and body temperature, were investigated before, during and after PE. Technical aspects of PE, i.e. arterial and venous blood flow rates, plasma flow rates, the consumption of anticoagulants and treated plasma volume, were analysed during each PE procedure. Thrombocytes, haemoglobin, LDH, calcium, potassium, albumin, liver enzymes, creatinine and clotting tests were performed before and after each PE.

To exclude viral transmission, hepatitis B, hepatitis C and HIV tests were performed once again 12 months after treatment.

Definition of Acute Renal Failure

Renal failure was defined as either an increase in serum creatinine to >0.5 mg/dl per day for 2 consecutive days or a serum creatinine level < 4.0 mg/dl and dialysis that began within 7 days of diagnosis.

Table 1. Data for individual patients

ID	Age, years	Sex	Etiology ^a	NS ^b	GCS	CSS	Ass. Dis	Hb, mg/dl	LDH, U/ml	Platelets × 10 ⁹ /l	Creatinine, mg/dl	PE: No	PE SE	VA ^d	VA SE ^e	Outcome/ months
1	39	M	I	2	9	6	Ca	6.4	1,400	16,000	0.8	4	0	Sh		R/4 †
2	67	M	G	2	10	5	Hep C	5.4	2,500	11,000	0.9	8	0	Sh		R/57
3	58	F	R	2	11	5		4.8	3,800	19,000	0.8	12	2	2× Sh	FE, SI	R/66
4	49	F	I	2	10	5		6.5	2,100	18,000	1.1	6	0	Sh		R/74
5	62	M	R	1, 2	10	6		5.1	1,800	17,000	3.4 ^D	13	0	2× Sh	FE, SI	R/59
6	50	M	R	1	9	5	Hep C	7.6	2,800	32,000	0.8	10	0	Sh		R/16
7	68	F	R	1, 4	8	6		8.8	3,500	21,000	0.8	13	0	Sh	LI	R/78
8	72	M	I	2	10	4		6.2	2,300	16,000	0.9	12	0	Sh		R/42
9	45	M	G	1, 2	10	5		7.2	2,875	10,000	1.8	13	0	Sh		R/28
10	75	F	G	1	15	6		6.9	1,080	19,000	5.4 ^D	12	0	Sh		R/31
11	63	F	R	1	13	4		5.8	3,400	11,000	0.8	12	0	Sh		R/34
12	48	F	I	3, 4	7	6	Ca	6.5	2,600	28,000	0.8	13	0	Sh		R/18 †
13	69	F	G*	3, 4	7	6		7.5	1,600	22,000	2.1 ^D	10	0	2× Sh	FE, SI	R/43
14	65	M	I	2	9	4	Ca	8.2	1,980	9,000	0.5	12	0	Sh		R/11 †
15	72	F	R	2	9	5		6.3	1,450	14,000	0.8	9	0	Sh		R/40
16	40	F	I	2	10	4	Ca	5.6	1,500	20,000	0.6	20	0	peripher		R/7 †
17	56	F	I	1, 2	9	4		5.3	2,800	11,000	0.8	5	0	peripher		R/21
18	39	F	G	1, 2, 3	6	5		6.5	1,800	18,000	0.8	23	1	Sh		3× relapse/96
19	35	F	R	1, 2	8	5		7.4	1,600	48,000	0.9	6	0	Sh		R/56
20	59	F	R	1	9	4		6.8	2,800	8,000	0.9	24	2	2× Sh	OC	R/38
21	60	M	I	1	10	4		8.1	1,950	22,000	0.9	8	0	Sh		R/53
22	54	M	G*	1, 4	7	8		5.6	3,500	6,000	0.9	18	0	Sh		R/42
23	43	F	I	1	10	3	Ca	6.7	1,100	22,000	0.9	12	0	Sh		R/25 †
24	38	F	R			4		5.8	1,700	4,000	0.9	6	0	Sh		R/82
25	39	M	G*			4		6.8	2,300	8,000	0.9	27	1	Sh		R/55
26	49	F	R			4		6.8	3,000	8,000	0.9	9	0	Sh		R/68
27	75	F	G*			6		7.9	1,500	8,000	4.5 ^D	50	3	3× Sh	FE, SI, OC	R/D/39
28	74	F	I	3.5	5	6		7.4	1,380	12,000	0.7	12	0	Sh		R/I/17
29	53	F	R	3.5	4	5		6.3	3,600	26,000	0.9	19	0	Sh	LI	R/I/34
30	46	M	R	2	9	5		7.2	2,875	10,000	1.3	13	0	Sh		R/23
31	43	F	G	2	9	5	WG	5.3	2,400	8,000	0.8	23	0	Sh		R/32

Ass.Dis = Associated disorder; CSS = clinical severity score [20]; GCS = Glasgow coma scale [19]; NS = neurological status on admission;

PE No = number of plasma exchanges; PE SE = plasma exchange side-effects; VA = type and number of vascular accesses; VA SE = vascular access side-effects;

^a G = gastrointestinal infection; I = Idiopathic; R = respiratory infection; * = EHEC-positive gastroenteritis.

^b 1 = dizziness; 2 = headache; 3 = apoplexia; 4 = cramps; 5 = coma.

^c Ca = Cancer; D = dialysis; Hep C = hepatitis C; WG = Wegener's granulomatosis.

^d Sh = jugular Sheldon catheter;

^e FE = fever; LI = local infection; OC = occlusion; SI = systemic infection.

^f D = dialysis, I = institutionalised; R = remission; † = death.

Definition of Severe Neurological Abnormalities

Severe neurological abnormalities were defined as coma, stroke, seizure, fluctuating focal signs, motor defects, diplopia or aphasia. On admission, neurological failures were scored by the Glasgow coma scale (GCS) as described elsewhere [19]. The GCS is scored between 3 and 15, with 3 being the worst and 15 the best. The GCS is composed of three parameters: best eye response, best verbal response and best motor response. A coma score of 13 or higher correlates with a mild brain dysfunction, 9–12 is a moderate brain dysfunction, and 3–8 is a severe brain dysfunction, often requiring artificial ventilation.

Definition of Clinical Severity Score

To assess a patient's disease severity, the Clinical Severity Score (CSS) which incorporates neurological, renal and haematological abnormalities,

ranking for each parameter from 0 (not severe) to 8 (severe), was documented. A CSS of 7 or 8 is associated with a poor prognosis, as validated in a large clinical study [4].

Plasma Exchange Techniques

Vascular Access

All central venous jugular catheters (Trilumen Sheldon) were inserted using the Seldinger technique under ultrasound guidance, as described by Gann and Sardi [20]. Continuous low-dose heparinisation (100–400 U/h, depending on the thrombocyte count, clinical situation and prothrombin clotting time) was performed to prevent thrombosis and occlusion. In 2 patients, treatment was performed via peripheral cubital veins.

Plasma Exchange Procedure

Before starting PE, all patients received an intravenous treatment with 100 mg of prednisolone and 0.67 mg of the H₁ antihistaminic clemastine hydrogen fumarate (Tavegil®, Novartis Consumer Health GmbH, Munich, Germany).

PE was initiated daily, plasma volume was exchanged completely with fresh frozen plasma (FFP; 15–18 U, 250 ml plasma/U). Treatment was continued until the platelet count was >150,000/μl and LDH values decreased to normal range. Peripheral blood smears were examined for the presence of schistocytes initially and at the end of the treatment. The count should then be <1%.

All procedures were performed by centrifugal plasma separation via a Cobe Spectra system (Cobe Spectra, Cobe Labs Inc., Lakewood, CO, USA, or Autopheresis-C® Therapeutic Plasma Systems, Baxter Healthcare Corp., Round Lake, IL, USA), with an automatic plasma-separating program as described elsewhere [16–18]. Blood was drawn at a rate of up to 70–80 ml/min via the biluminal central venous catheter in case of inefficient peripheral vascular access. During PE, citrate (acid-citrate-dextrose (ACD-A), Baxter Healthcare Corp.) was used as the sole anticoagulant, diluted 1:30 to 1:40 (v/v) in patients with thrombocytopenia < 30,000/μl.

To avoid citric reaction, a solution of 10% (w/v) calcium gluconate at a dose of 1.84–2.76 mmol/h was administered into the lumen of the return line during therapy. Doses were adapted to clinical symptomatology. The blood was warmed to body temperature during the return passage when patients were not febrile.

The PE procedure was started when initial blood pressure was >90 mm Hg; otherwise, crystalline solution and/or catecholamine were given before treatment.

Definition of Clinical Outcome

The desired response to treatment was defined as the normalization of the platelet concentrations during PE within 1 week after the end of treatment. Remission was defined as normal blood parameters without the requirement for further PE for >30 days. Relapse was defined as the recurrence of TTP/HUS following remission [21]. Mortality was regarded as being associated with PE if it occurred within 30 days after the end of the PE treatment [21].

Data Analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 12.0 (SPSS, Inc., Chicago, IL, USA). The primary study endpoints were defined as end of PE and complete remission. The median time to reach these endpoints was calculated on the basis of the associated 95% confidence intervals (95% CI).

Non-parametric statistics: the Mann-Whitney U-test was used to determine differences between vegetative parameters before and after PE treatment.

Results

Patient Characteristics

From January 2000 to January 2005, 31 patients with suspected TTP (11 males, 20 females) were treated in our centre with PE during the initial episode of the disease. A total of 27 patients were diagnosed as having solely TTP. In 4 patients also symptoms of HUS were found; the neurological symptoms were accompanied by renal insufficiency requiring dialysis.

Fig. 1. Treatment endpoints were reached rapidly in our patients.

Kaplan-Meier plot of the number of PE treatments until complete remission. The median number was 12 therapies (95% CI, 10–14 PE therapies). The abscissa shows the number of PE treatments. Numbers above the Kaplan-Meier curves represent patients completing the therapy within the corresponding period of time. Vertical excursions of the curves signify the occurrence of events.

The median age was 55 years (range 35–75 years; mean 54 ± 12.6 years). The following neurological symptoms were observed (summarized in table 1): i) dizziness $n = 13$, ii) headache $n = 14$, iii) apoplexy $n = 5$, iv) cramps $n = 4$, v) coma $n = 2$. The median GCS of patients on admission was 9 (range 4–15; mean 9.0 ± 2.2). The median CSS on admission was 5 (range 3–8; mean 5 ± 1.0).

A total of 12 patients had a history of respiratory infections. Gastrointestinal infections were seen in another 9 patients, with 4 being tested positive for EHEC. In 10 patients, the disease was idiopathic.

Co-morbidities were found in 8 patients. Five of them suffered from cancer (mammary cancer (patient 16), small-cell lung cancer (patient 1), T-cell lymphoma of the skin (patient 14), stomach cancer (patient 12) and oesophageal cancer (patient 23)). The other 3 patients had immunological co-morbidities, namely Wegener's granulomatosis (patient 31) and hepatitis C infection (patient 2 and patient 6).

Laboratory Parameters

The median haemoglobin level on admission was 6.5 mg/dl (range 4.8–8.8 mg/dl; mean 6.6 ± 0.9 mg/dl). A median of 2 blood units was substituted during crisis (range 0–9 units; mean 2.3 ± 1.8 units).

The median LDH level on admission was 2,300 U/ml (range 1,000–3,800 U/ml; mean $2,990 \pm 790$ U/ml).

The median thrombocyte level on admission was 16,000/ μ l (range 4,000–48,000/ μ l; mean $16,193 \pm 9,098$ / μ l). Schistocytes were visible in all blood smears. Their count varied between 3 and 18%.

Plasma Exchange

PE was started 12–24 h after admission and diagnosis. 434 PE procedures were performed. A median number of 12 PE therapies (95% CI 10–14 PE therapies) was necessary to achieve complete remission (fig. 1). Patient 25 and patient 27 required PE twice daily for 2 days.

A median of 3.7 l of plasma was exchanged by FFP (range 3.0–4.2 l; mean 3.7 ± 0.2 l).

Complications and Side-Effects of Plasma Exchange Procedures

Minor and major complications and side-effects of PE procedures are shown in tables 1 and 2. Under pre-medication with steroids and antihistamines, only a few side-effects were observed (table 2). None of our patients developed allergic reactions. No fatality was seen during 434 PE procedures. The 2 patients (patient 17 and patient 25) who developed a slight decrease of blood pressure responded well to volume substitution (table 2).

Mild citric reactions (paraesthesia, tremor) occurred in 3 patients. An increase of the calcium gluconate substitution diminished these reactions immediately.

There was no platelet loss due to the extracorporeal system. The median platelet concentration during the first four PEs was 48,000/ μ l (range 12,000–87,000/ μ l, mean $49,000 \pm 37,509$ / μ l). None of the PE treatments required interruption. There were no major complications during PE.

Complications and Side-Effects of the Central Venous Access

Minor and major complications of the central venous vascular accesses are shown in tables 1 and 2. A total of 29 patients received a central venous jugular tri-lumen catheter; a peripheral vascular access was possible in 2 patients. All catheters were implanted under visual ultrasound guidance. No faulty insertion was seen. In 5 patients, the catheter had to be replaced due to infection or occlusion after a median of 16 days of insertion (range 10–18 days). Infections that occurred after a median of 14 days (range 12–16 days) responded well to antibiotics and changes of vascular access. The blood cultures of these patients were positive for *Staphylococcus epidermidis* and *Staphylococcus aureus*, and the same species were detectable in the smears from the Sheldon catheter entrance

side. Although all patients received low-dose heparin in the presence of thrombocytopenia, no severe bleeding occurred. Overall, 35 central venous catheters were inserted without complication.

Hospitalisation and Treatment Duration

At the beginning of the PE therapy, 9 patients were supported by mechanical ventilation (MV) due to respiratory problems induced by TTP. The median stay at the ICU was 20 days (range 18–30 days; mean 22 ± 3 days), the median duration of MV was 18 days (range 8–180 days; mean 28 ± 37 days), and the median stay in hospital was 32 days (range 18–65 days; mean 32 ± 19.8 days).

Clinical Outcome and Relapses during Long-Term Follow-Up

None of the patients died due to TTP/HUS. During the long-term follow-up (mean 41.6 ± 23.3 months, median 39 months, range 4–96 months), 30 patients achieved a complete remission. One young female patient experienced 3 relapses during the long-term follow-up. The first relapse occurred 2 years after the first TTP episode and happened 3 days after childbirth. The relapse was again treated successfully with PE. The 2nd and 3rd relapse occurred 12 and 18 months later, respectively, during a gastrointestinal infection. Since a high inhibitory antibody titre against ADAMTS13 was detectable, the patient was treated initially with PE and received an immunomodulatory regime combined with immunoadsorption and azathioprine until ADAMTS13 antibodies were no longer detectable. Treatment with azathioprine is still ongoing since several attempts to discontinue azathioprine led to the occurrence of neurological symptoms (severe headache). During the 5-year follow-up, the patient experienced no further TTP crisis. In patients suffering from cancer ($n = 5$), TTP was diagnosed in an advanced tumour stage before chemotherapy was initiated. The patients responded well to PE, but all died during the long-term follow-up due to tumour progression.

Four patients developed renal insufficiency during TTP/HUS and had to undergo dialysis for a median of 18 days (range 12–20 days), 3 patients were weaned off dialysis. The neurological symptoms improved in 25 patients; however, 2 patients needed to be institutionalised due to apoplectic insults. Controls of the infection status demonstrated that no virus transmission occurred during PE therapy.

Discussion

All of our 31 patients suffered from severe TTP syndrome, as indicated by a mean CSS of 6 points and a GCS of 9 points. Well-known triggering mechanisms for TTP are infections,

Table 2. Major and minor complications of plasma exchange treatment and catheter implantation

	Patients		
	Own data	McMinn et al. [14]	Rizvi et al. [13]
<i>Complications of plasma exchange (PE)</i>			
Number of PEs	434	n.g.	884
Minor complications			
Urticaria	0/31	22/78	22/71
Tetany	0/31		3/71
Tremor	1/31		
Hypotension (requiring volume substitution)	2/31		10/71
Paresthesia	2/31		
Percentage	16 (5/31)	28 (22/78)	49 (35/71)
Major complications			
Anaphylaxis with cardiac arrest	0/31	1†/78	
Hypotension	0/31	2/78	
(requiring dopamine)	0/31	1/78	
Serum sickness	0/31	1/78	1/71
Hypoxia (requiring steroids)	0/31	2/78	2/71
Vomiting (interrupting PE)	0/31	1/78	
Percentage, %	0 (0/31)	10.2 (8/78)	4.2 (3/71)
Outcome			
Number of relapses	3		12
Patients with relapses	1 (3%)		8 (11%)
Mortality	0	3	3
<i>Complications of central venous catheters</i>			
Number of insertion procedures	35	n.g.	49
Minor complications			
Local bleeding	2/35	2/78	
Obstruction	0/35	8/78	
Local infection at catheter site	2/35	7/78	7/71
Percentage, %	11 (4/35)	21 (17/78)	9.8 (7/71)
Major complications			
Pneumothorax and haemorrhage	0/35	1†/78	2/71(1†)
Cardiac tamponade	0/35	1†/78	
Retroperitoneal haemorrhage	0/35	1/78	
Systemic infection	4/35	10/78	12/71(1†)
Thrombosis (requiring anticoagulation)	0/35	2/78	2/71
Obstruction (requiring catheter removal)	2/35	5/78	7/71
Percentage, %	17 (6/35)	26 (20/78)	32 (23/71)
n.g. = Data not given; † = death.			

mainly gastrointestinal [21]. In our study, 9 patients suffered from gastroenteritis, which was EHEC-positive in 4 cases. Respiratory infections were confirmed anamnestically in 12 patients, and 2 patients suffered from hepatitis C infection. Thus, infections could be identified as the triggering mechanism in the majority of patients.

Similar to other acquired coagulating disorders, e.g. acquired haemophilia A [16–18], an association with cancer was seen in 5 of our patients. In these patients, TTP preceded the diagno-

sis of cancer and was not induced by chemotherapeutical drugs. These patients responded to PE but died during the follow-up period due to their advanced cancer disease.

Recent advances in the understanding of the pathophysiology of TTP underline the relevance of ULvWF multimers and ADAMTS13 deficiency in the disease pathogenesis [1, 21, 22]. vWF is synthesized and released from endothelial cells and megakaryocytes. The vWF multimers that are immobilized on the activated endothelial cells and unfolded by high shear

stress then undergo proteolysis by ADAMTS13. Severe deficiency of ADAMTS13 is followed by an anchorage of ULvWF on the surface of endothelial cells. In contrast to smaller vWF conjugates, platelets adhere strongly to the ULvWF, resulting in platelet aggregates forming occlusive platelet thrombi in the microcirculation. PE treatment removes large amounts of multimers and substitutes simultaneously the cleavage enzyme ADAMTS13 [23, 24]. Therefore, the general success of PE treatment decreasing the disease mortality from 90 to 10–35% is not astonishing [4, 9]. In addition, PE eliminates neutralising and non-neutralising antibodies rapidly. This will undermine the immunological follow-up reactions, e.g. the shift of the inhibitor class from unspecific short-lived IgM to highly specific long-lasting IgG antibodies. The IgM antibodies will be depleted very efficiently by PE since they are readily accessible in the vascular space due to their pentameric structure [25, 26].

However, discrepancies between the levels of ADAMTS13, the presence of inhibitor and the response to PE have been reported [27]. One reason might be that current assays are not sufficiently sensitive for complete detection of the inhibitor [5]. Alternatively, mechanisms of inhibitor interactions with their antigens can be different [1].

Scheiflinger et al. [27] reported the improvement of antigen clearance without antigen inhibition via so-called non-neutralising antibodies of IgM and IgG subclasses in a patient with fatal TTP. Also, the clinical manifestations of severe ADAMTS 13 deficiency, either congenital or acquired, are heterogeneous [5]. They range from no or minimal symptoms and signs to progressive multiple organ failure, suggesting that many factors contribute to acute episodes [28].

Even though the use of concomitant glucocorticoid therapy is not supported by data from randomised trials, the addition of steroids to PE is judged to be attractive [3, 5]. Based on findings of a functional deficiency of a novel vWF cleavage protease activity, adjuvant corticosteroids have been recommended [3]. This concomitant steroid therapy will undermine the antibody switch to more specific IgG, which is much more difficult to treat at a later stage [27]. As already mentioned, PE removes circulating antibodies and provides exogenous ADAMTS13 activity [8]. The rapid depletion of inhibitor combined with a substitution by 100% intact antigen, being available in FFP [29], is likely to advance the PE procedure to an immunomodulatory treatment regime.

Fontana et al. [8] reported recently a sequential treatment regime consisting of PE for 3 days and then a switch to protein A immunoadsorption for the days 4–6. They showed that the removal of autoantibodies from a patients' plasma was not sufficient to restore ADAMTS13 activity. Treatment strategies therefore should combine antibody removal with the substitution of ADAMTS13. A recombinant ADAMTS13 is under investigation in animal studies, but is not yet available for human treatment [12]. Furthermore, immunoadsorption does not remove ultralarge multimers. Therefore, immunoadsorp-

tion as first-line therapy may be insufficient to regain haemostasis.

There have been only a few reports concerning complications of PE during TTP treatment. The overall complication rate is reported to be 61%, and major complications were detected in 30% of the cases [13], which is still very high. Allergic and anaphylactic reactions can occur and are often difficult to control during PE, due to the permanent dilution of emergency medication. Our patients received a uniform pre-medication with steroids and H1-antihistamines just before each treatment to prevent allergic and anaphylactic reactions. In 434 PE procedures, none of our patients developed allergic reactions. In contrast, Rizvi et al. [13], McMinn et al. [14] and Reutter et al. [30] described urticarial reactions in 28–68% of patients, even leading to one instance of fatal anaphylactic shock [14]. The concomitant steroid treatment did not increase the systemic infection rate. In contrast to Rizvi et al. [13] who described a systemic infection rate of 12%, only 3 of 35 catheter insertions (8.5%) were complicated by infections in our study. Another challenge of the PE procedure is the large amount of citrate that is applied by the FFP (containing in median 10% ACD-A). Our procedure to reduce anticoagulation by continuous substitution of calcium gluconate via the return line from the start of treatment onwards and warming the blood in non-febrile patients was successful in reducing the clinical signs of citric reactions to less than 10%. The symptoms were minor and did not require interruption of PE. They were treated easily by adapting the calcium substitution to the clinical symptoms. Severe bleeding complications under PE were not seen, even in patients with extremely low thrombocyte counts ($<10,000/\mu\text{l}$).

The loss of up to 71% of thrombocytes [4] in the extracorporeal system during PE is another technical problem that complicates treatment in severe TTP, especially in patients with very low thrombocyte counts. In addition, unintentional platelet removal can mask the success of PE treatment. In our study, thrombocyte counts were determined before and after the first PE and showed a minimal increase that was not statistically significant. This finding supports data from other studies reporting that the centrifugal plasma separation technique is superior to other apheresis procedures [4, 29]. Furthermore, the centrifugal separation technique is applicable without additional heparinisation, which is another clinical advantage of this separation technique in the treatment of TTP. Due to these factors, none of our patients experienced a life-threatening haemorrhage, which would make the application of thrombocyte concentrates necessary, a procedure being contraindicated in TTP [3].

Up to 50% of patients are reported to have major complications due to the central venous catheter implantation. McMinn et al. [14] described 2 fatalities due to a displacement of the catheter. Severe thrombocytopenia can induce bleeding complications, and some authors recommended the substitution of high-dose recombinant factor VIIa, which may help to

establish haemostasis via a faster platelet activation compensating for the lower number of platelets [34].

In our patients, 35 central venous jugular catheters were implanted without major complications using the Seldinger technique under ultrasound guidance. These results support data of other studies to prefer this implantation technique [20], especially in high-risk patients. Compared to the data reported by Rizvi et al. [13] and McMinn et al. [14] showing 4 catheter-associated fatalities, the venous jugular catheters which are preferred in our study appear to be a safe vascular access. As the use of anti-platelet agents in TTP remains controversial [5], we decided to use continuous low-dose heparinisation. This decision appeared to be successful in preventing catheter occlusions and thrombosis (2/35 versus 15/78 [14] versus 9/71 [13]). With respect to the beneficial systemic effect of low-dose heparin in treatment and outcome of TTP, it can only be speculated that its vasodilative effect induced by the inhibition of the endothelin-1 production [35] combats the effects of vessel blockage in the microcirculation during TTP. Another mechanism might be that the partial inhibition of the thrombin generation reduces the procoagulatory capacity of the pa-

tients' plasma, without increasing the general bleeding risk, despite extreme thrombocytopenia.

In summary, remission from TTP was achieved in 30 of 31 patients. There was no TTP-associated mortality. The relapse rate was extremely low (3%), demonstrating that long-term immunotolerance was achieved. This supports the idea that this protocol has immunomodulatory potency. However, our results should be confirmed in a larger cohort of patients.

Conclusion

Prophylactic pre-medication with steroids, treatment with antihistamines and concomitant calcium substitution lead to a good compatibility of PE. Centrifugal plasma centrifugation systems are especially successful in thrombocytopenic patients. The insertion of the jugular central venous catheter using the Seldinger technique under ultrasound guidance is extraordinarily safe; occlusions are best protected by continuous flow of low-dose heparin. Our protocol showing a very low complication rate is a safe treatment regime for severe TTP.

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