Plasma and Whole Blood Exchange in Meningococcal Sepsis

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The present study describes the effect of plasma exchange or whole blood exchange (PEBE) on the survival rate among patients with fulminant meningococcal sepsis and on the level of circulating endotoxin. Since 1989 all patients with meningococcal disease and hypotension who were admitted to our intensive care unit were treated with PEBE. Results for our patients were compared with those for a historical control group conventionally treated between 1984 and 1989 (n=10; mortality rate, 60%); the expected mortality rate, which was based on the Niklasson prognostic score and was calculated for seven patients in this control group, was 73%. A total of 15 patients were treated with PEBE, three (20%) of whom died, whereas the prognostic score (calculated for 14 patients) for this group was 62%. In two of the fatal cases, PEBE was started after a delay of ≥40 hours. In the remaining 13 patients, PEBE was started within 5–30 hours after the first hospital admission. The mortality rate among this group was 8% (one of 13 patients); this rate was significantly different from that among the control group (P= .025). For seven patients treated with PEBE, plasma endotoxin concentrations were sequentially measured. The overall half-life (± SEM) of endotoxin was 181 ± 18 minutes. This is approximately the same as reported values for patients who were not treated with PEBE. It is concluded that early initiation of PEBE may improve the rate of survival among patients with meningococcal infection and hypotension but that the mechanism of the beneficial effect is most likely not based on the elimination of endotoxin.

Neisseria meningitidis invading the bloodstream can lead to different disease manifestations [1]. After a 1- to 2-day flulike illness, acute meningitis may develop with signs of meningeal inflammation without shock. The mortality rate associated with this disease is ~1% [2]. On the other hand, in patients with fulminant meningococcal sepsis (FMS), severe shock develops within a few hours, often with diffuse intravascular coagulation; signs of meningeal inflammation are minor or absent. The mortality rate associated with FMS is high, varying from 30% to 70%, even if intensive treatment is started immediately [2–6]. Approximately 90% of all fatal cases of FMS occur in patients who present with hypotension [2, 7]. According to most studies [8–12], other signs of a poor prognosis on admission are the absence of meningeal inflammation, the presence of rapidly extending hemorrhagic skin lesions, hyperpyrexia, leukocytopenia, thrombocytopenia, hypofibrinogenemia, diffuse intravascular coagulation, metabolic acidosis, and rapid clinical deterioration. Multifactorial scoring systems, combining the above-mentioned factors, have been developed to predict outcome and to distinguish patients who merit intensive or, in severe cases, even experimental treatment [7, 8, 10, 12]. In severe cases of FMS, it has been suggested that plasma exchange (PE) or whole blood exchange (BE) in addition to standard therapy reduces mortality [13–16], possibly by accelerating the elimination of endotoxin [17].

For editorial response, see pages 431–3.

In the last decade, the proportion of patients with FMS in the Netherlands has steadily increased, and since 1989 the incidence of all meningococcal infections has doubled. In view of the poor results of conventional treatment in the preceding years, in 1989 we began to perform PE or BE (PEBE) in addition for patients with hypotension due to meningococcal infection.

In the present paper, we describe our experience with PEBE and compare the results of treatment with those for a historical control group of patients who were admitted to the hospital before 1989. The changes in the concentrations of endotoxin during PEBE are also reported.

Methods

From 1984 to 1992, 43 patients with meningococcal infections were admitted to the intensive care unit (ICU) of the University Hospital Nijmegen. Of these patients, 27 presented with hypotension, which was defined as the following systolic blood pressures: adults, <100 mm Hg; children <4

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years old, <75 mm Hg; and children ≥4 years old, <85 mm Hg. This latter group of 27 patients will be discussed herein. The bacteriologic diagnosis was confirmed by culture of CSF, blood, or specimens of skin lesions in 24 cases and by serology in two. In one case culture results were lost, but the diagnosis was clinically evident. Until 1989 10 patients were treated "conventionally," i.e., with fluids, inotropic and vasoactive drugs, antibiotics, steroids, mechanical ventilation, and, if necessary, hemodialysis or peritoneal dialysis. In addition to conventional treatment, two patients underwent continuous arteriovenous hemofiltration (CAVH). Since 1989 PEBE was performed or was intended to be performed for 15 patients. In each PE session, 30–40 mL of plasma per kilogram was exchanged with fresh frozen plasma. The procedure, which took 1.5–2.0 hours, was started as soon as possible after admission and was repeated after 12 hours and, if the condition of the patient was still critical, after 24 and 48 hours. In children whose body weight was <25 kg, BE was performed with 50–60 mL of whole blood per kilogram, following the same schedule. Each session took 0.6–1.5 hours.

For determination of concentrations of endotoxin, 2-mL plasma samples were taken in 5-mL pyrogen-free plastic vials (Falcon, Becton and Dickinson, Lincoln Park, NJ) containing 50 U of pyrogen-free heparin per milliliter, centrifuged at 200*g* for 10 minutes, and stored at −70°C until assay. The concentration of endotoxin was measured with use of a chromogenic Limulus amebocyte lysate assay (KabiVitrum, Stockholm). For statistical analysis, a Wilcoxon's test and adjusted χ^2 test were used. Log-linear regression was used to calculate the elimination kinetics of endotoxin.

Results

Characteristics and Prognostic Values at Admission

Eight patients were directly admitted to our ICU, and 19 were referred from local hospitals. Clinical and laboratory values at hospital admission and their prognostic significance are listed in table 1. Patients 1–10 were treated conventionally, patients 11 and 12 underwent CAVH in addition to conventional treatments and patients 13–27 underwent PEBE, as specified in table 2. All patients had skin lesions of abrupt onset (existing <6 hours). Large, extending ecchymoses that were >1 cm in diameter were seen in all patients except 12 and 27; in these two, only small purpural lesions were observed. Median values of age, preclinical disease period, blood pressure, leukocyte count in CSF, leukocyte count in peripheral blood, platelet count, and concentrations of bicarbonate, base excess, and fibrinogen are given in table 1. These values did not differ significantly between both groups ($P \geq .22$). Of the 19 referred patients, 15 were referred within 12 hours because of progressive shock. Patients 11, 23, and 25 were referred after a delay of 56, 26, and 59 hours, respectively, because of shock, anuria, and overhydration. The delay in time to referral in the conventional treatment group was shorter than that in the PEBE group, but this difference was not significant ($P = .22$) (see table 2).

Treatment and Outcome

The primary treatment of all referred patients was started in the referring hospital. Hence, there was no uniformity in the treatment during the first hospitalization. All patients, except patients 2 and 27, received pharmacological doses of glucocorticosteroids on admission.

After arrival at our ICU, patients 1–10 were conventionally treated; six of these patients died. One of the survivors (patient 8) underwent amputation of three toes and fingertips and suffered from complete sensorineural deafness.

Patients 11 and 12 underwent CAVH in addition to conventional treatment and are included in the present series for the sake of completeness; one of these patients died. This patient was referred to our ICU after a delay of 56 hours because of multiple organ failure (MOF), anuria, and gangrene of both lower legs. CAVH was started after 74 hours. Four days later cerebral death was noted. In patient 12 CAVH was started 6 hours after the first hospitalization and continued for 52 hours; this patient completely recovered.

In patients 13–27 PEBE was done or was intended to be done; three of these patients died. Patient 22 arrived at our ICU after a delay of 11 hours and was noted to be in severe shock with metabolic acidosis (pH, 7.27; bicarbonate concentration, 16.9 mmol/L; base excess concentration, −9.2 mmol/L), diffuse intravascular coagulation (fibrinogen concentration, 840 mg/L; fibrinolytic split product concentration, 240 mg/L; platelet count, 22×10^9/L), and acute renal failure (serum creatinine, 305 μmol/L). He died of internal bleeding due to an iatrogenic perforation of the subclavian vein shortly before the intended PE could be started. In patient 13 and 25, PE was started 40 and 74 hours, respectively, after the first hospital admission because of technical problems and delayed referral. Both patients had been hypotensive for >12 hours before PE was started and at the time of its initiation had severe MOF, probably with cerebral damage. After the presence of severe cerebral damage was established and treatment was withdrawn, these patients died. In the 12 other patients, PEBE was started within 5–30 hours after the first hospital admission and within 2–13 hours after arrival at our ICU. All recovered without serious sequelae, but three needed plastic surgery for necrotic skin areas. During the exchange procedure, no adverse effects were observed.

For seven patients the concentration of endotoxin was monitored during PEBE (figure 1). The endotoxin concentration correlated with the clinical severity of disease. Plasma endotoxin concentrations decreased at a more-or-less constant rate during the first 18 hours. The half-life ($t_{\frac{1}{2}}$; ± SEM)

Table 1. Patient characteristics on admission with prognostic significance.

Patient no.	Sex/age (y)	Preclinical disease period (h)	Blood pressure (mm Hg)*	Central temperature (°C)	Leukocyte count in CSF ($\times 10^6$/L)	Leukocyte count in peripheral blood ($\times 10^9$/L)	Platelet count at 0 and 4 h† ($\times 10^9$/L)	Concentrations of	
								HCO_3^-/base excess (mmol/L)	Fibrinogen/ fibrinolytic split products (mg/L)
1	F/0	14	50/40	39.9	46	10.0	67/67	12.5/−14.7	540/70
2	F/0	2	xx/xx	38.3	13	3.3	151/—	11.8/−14.4	1,700/—
3	F/3	8	xx/xx	39.7	72	7.5	123/—	12.5/−11.8	—/—
4	F/6	6	75/60	—	6	4.3	150/72	12.4/−10.0	—/—
5	M/8	16	60/30	—	—	14.6	56/46	17.6/−7.2	1,380/180
6	F/11	9	85/35	40.1	52	15.7	138/120	21.3/−4.6	2,295/<10
7	M/17	10	90/70	39.5	—	4.8	19/14	13.5/−11.2	450/1,024
8	M/21	25	80/40	40.1	—	14.6	68/48	10.7/−9.7	1,355/855
9	M/23	15	xx/xx	39.0	40	7.5	39/—	10.5/−13.5	<600/—
10	F/31	20	90/60	38.0	2400	24.5	173/161	17.8/−4.7	3,950/<10
1–10 (median)	9.5	12	68/38	39.6	46	8.8	96/67	12.5/−10.6	1,318/—
11	F/17	6	50/xx	40.6	240	4.1	55/30	12.0/−10.0	900/180
12	M/22	16	xx/xx	40.8	68	3.7	119/127	18.5/−4.7	4,500/<10
13	M/0	6	xx/xx	39.4	6	5.9	122/18	11.0/−21.0	300/33
14	F/1	3	70/xx	39.5	120	11.8	196/162	14.0/−5.9	3,055/<10
15	F/1	7	60/40	39.4	20	11.0	196/98	15.9/−6.2	—/—
16	M/3	9	68/35	41.8	175	2.8	192/82	14.9/−8.3	230/>240
17	M/4	19	60/40	—	13	19.2	123/61	11.6/−17.8	1,565/20
18	F/5	16	80/50	40.7	11	7.3	231/212	13.3/−9.1	3,732/<10
19	M/8	6	80/50	41.2	14	3.3	114/85	19.0/−4.8	3,500/20
20	F/9	10	75/40	40.0	3	2.5	66/70	14.2/−10.2	1,665/55
21	M/11	7	75/50	41.8	45	2.0	79/58	17.0/−5.0	1,465/50
22	M/11	2	75/50	39.0	98	7.0	125/43	—/—	<500/170
23	F/14	9	75/30	40.2	—	2.8	95/71	14.0/−10.0	—/220
24	F/15	9	xx/xx	—	1370	21.4	122/65	11.5/−15.5	1,800/65
25	M/15	12	95/65	39.8	12	4.5	61/38	11.0/−15.0	650/180
26	M/21	23	85/60	38.7	1250	15.3	122/66	21.0/−1.7	4,115/<10
27	F/33	18	xx/xx	38.7	4250	18.0	189/105	18.9/−4.6	4,515/<10
13–27 (median)	9	9	75/40	39.8	33	7.0	122/70	14.1/−8.7	1665/—

NOTE. Patients 1–10 were conventionally treated, patients 11 and 12 underwent CAVH in addition to conventional treatment, and patients 13–27 were treated with PEBE. — = missing values.

* xx/xx indicates that blood pressure was unmeasurably low.

† Time calculated from (first) hospital admission.

ranged from 77 ± 3 minutes for patient 18 to 245 ± 27 minutes for patient 14. On the basis of the assumption that kinetics were similar for all seven patients, the overall $t_{\frac{1}{2}}$ was 181 ± 18 minutes. An accelerated decrease in endotoxin concentrations during the first PEBE session was observed for only four of seven patients.

Discussion

The present study describes the course and outcome of meningococcal infection in patients with hypotension who were treated with PEBE.

Hypotension is considered to be one of the most reliable and strong predictors of a poor prognosis in meningococcal disease [2]. Gårdlund [7] reported a mortality rate of 42% among patients (all ages) who were admitted with a systolic blood pressure of <100 mm Hg [7]. Using more strict criteria for hypotension in children (<70 mm Hg for children younger than 12 or 14 years of age), other authors reported mortality rates varying from 19% to 53% among hypotensive patients [2, 8, 18]. In this study, we have defined hypotension as a systolic blood pressure of <100 mm Hg in adults [2, 7, 8], <75 mm Hg in children <4 years of age, and <85 mm Hg in children ≥4 years of age [10, 12]. It should be kept in mind, however, that the systolic blood pressure can remain nearly normal for a long time even in the presence of severe shock, especially in children.

The presence of more factors predicting a poor prognosis increases the chance of a fatal outcome. According to Niklasson et al. [8], unfavorable prognostic features on admission are (1) the absence of meningitis (leukocyte count in CSF, $<100 \times 10^6$/L), (2) the presence of hypotension (systolic

Table 2. Course, treatment, and outcome for all patients.

Patient no.	Delay in time to referral*† (h)	Treatment (no. of sessions)	Time to start of first PEBE after admission† (h)	Outcome (time to death)	Expected mortality rate according to Niklasson score‡
1	—	Conventional		Died (4 h)	88%
2	3	Conventional		Died (4 h)	88%
3	2	Conventional		Died (4 h)	88%
4	3	Conventional		Died (14 h)	Not evaluable
5	6	Conventional		Survived	Not evaluable
6	—	Conventional		Survived	73%
7	10	Conventional		Died (14 h)	Not evaluable
8	—	Conventional		Survived	88%
9	—	Conventional		Died (6 h)	88%
10	—	Conventional		Survived	<73%
1–10 (median)	3				
11	56	Conventional plus CAVH		Died (7 d)	88%
12	1	Conventional plus CAVH		Survived	88%
13	6	PE (3)	40	Died (52 d)	88%
14	5	BE (2)	10	Survived	<73%
15	24	BE (2)	30	Survived	88%
16	8	BE (3)	11	Survived	88%
17	—	BE (3)	6	Survived	73%
18	1	BE (2)	5	Survived	88%
19	12	PE (4)	16	Survived	88%
20	2	BE (1), PE (2)	15	Survived	88%
21	7	PE (3)	10	Survived	88%
22	11			Died (12 h)	<73%
23	26	PE (3)	30	Survived	88%
24	3	PE (4)	5	Survived	Not evaluable
25	59	PE (3)	74	Died (11 d)	88%
26	—	PE (3)	5	Survived	<73%
27	—	PE (2)	5	Survived	<73%
13–27 (median)	7.5				

* Bar (—) indicates directly admitted to the ICU.
† Time calculated from the first hospital admission.
‡ See [8].

blood pressure, <100 mm Hg in adults and <70 mm Hg in children up to 14 year old), (3) the presence of petechiae for <12 hours, (4) hyperpyrexia (rectal temperature, >40°C), (5) the absence of leukocytosis (leukocyte count in blood, $<15 \times 10^9$/L), and (6) the presence of thrombocytopenia (platelet count, $<100 \times 10^9$/L). When three or four of the first four prognostic signs were present, the mortality was 73%; the presence of four or five of the first five signs resulted in a mortality rate of 88%. The individual prognoses of our patients' conditions were based on this scoring system and are given in table 2.

In our study, the observed mortality rate among the group treated conventionally was 60% (6 of 10 patients). This is approximately the same as the expected mortality rate calculated with use of the score of Niklasson. For seven patients this score could be calculated, and the expected mortality rate was 88% for five, 73% for one, and <73% for another. Therefore, for this group the expected mortality was at least 73% (5.13 of 7 patients), and the observed mortality among this group was 57% (4 of 7 patients).

In the literature, PEBE has been shown to reduce mortality. In 1979 Scharfman et al. [19] were the first to report a beneficial effect of PE for a patient with FMS. Meanwhile, 24 cases of patients who were treated with PEBE or plasmapheresis and leukapheresis were reported; five (21%) of these patients died [13–16, 19, 20]. Despite the observation that PE had no beneficial effect in six dogs with *Escherichia coli* sepsis [21], several authors underlined the possible value of this treatment for FMS [6, 22]. However, no controlled studies are available, probably because of the rare incidence of the disease and the inhomogeneity of clinical presentation. In this study, the mortality rate among the group treated with PEBE was 20% (3 of 15 patients). For 14 of these patients, the expected mortality rate according to Niklasson could be

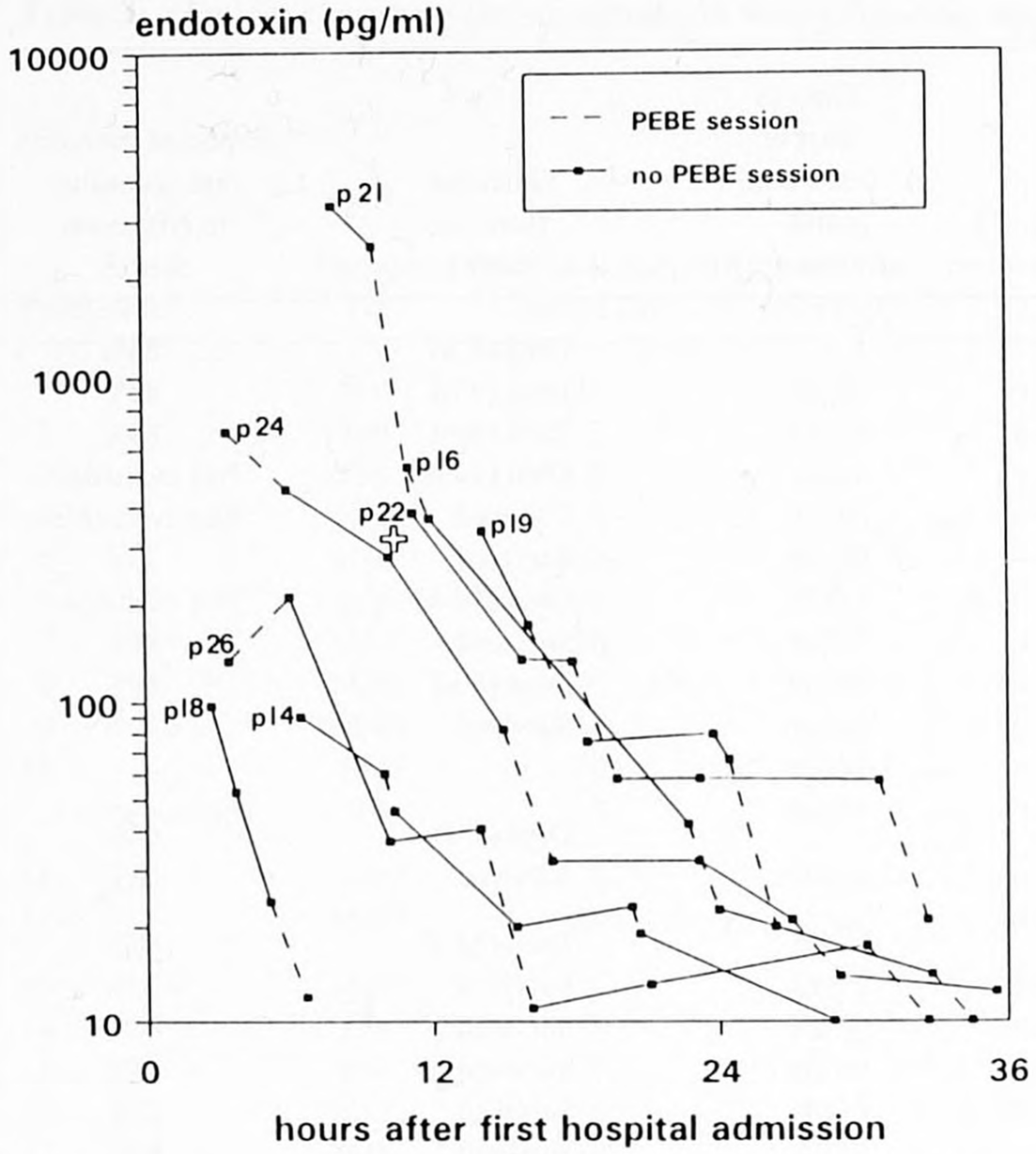

Figure 1. Concentrations of endotoxin during the first 36 hours after the first hospital admission for eight patients (14, 16, 18, 19, 21, 22, 24, and 26) treated with PEBE. PEBE sessions are indicated with dotted lines. Patient 22, indicated with a cross (+), died shortly after the first blood sampling, just before PE could be started. Abbreviation: p = patient.

calculated and was 62% (8.65 of 14 patients), with an observed mortality rate among these patients of 21% (3 of 14 patients).

PEBE is believed to be beneficial only when it is performed during an early phase of the disease. In two patients in this study, PEBE was started >40 hours after the initial admission. At that time, severe MOF and probably cerebral damage were already present. After the presence of extensive cerebral damage was established and treatment was withdrawn, both patients died. Obviously, PEBE was started too late. The remaining 13 patients were treated or were intended to be treated with PEBE within 30 hours after admission. This group did not differ significantly from the historical control group with respect to the prognostic factors (see table 3). Yet, among this group the observed mortality rate was only 8% (1 of 13 patients) compared with a mortality rate of 60% among the historical control group ($P = .025$) and an expected mortality rate (calculated for 12 patients) of 57% (6.89 of 12 patients).

Some facts may have flattered these results. It is known that 70% of the patients with fatal cases died within 16 hours after admission [3–5, 8, 23, 24]. Table 3 shows that in the PEBE group more patients were referred and that the delay in time to referral was longer. This may reflect patient selection, as dramatically ill patients died before referral was organized. Also, some of the other prognostic factors summarized in table 3 show a slightly better prognosis for the PEBE group; however, none of these differences were significant. Finally, the comparison with a historical control group may be criticized. Dagbjartsson and Ludvigsson [25] reported a lower mortality during the later phase of an epidemic possibly because of better awareness of the public or treatment by better-skilled doctors. Nevertheless, it is our impression that certain patients who were in deep shock at entry into our ICU clearly benefitted from PEBE. In the conventionally treated group, all patients without leukocytosis (leukocyte count in blood, $\leq 10 \times 10^9$/L) and/or a base excess concentration of ≤ -10.0 mmol/L died. In the PEBE group, eight of nine patients with these poor prognostic signs survived. These figures support the conclusion that in patients with FMS early initiation of PEBE may improve outcome, but clearly a controlled study is necessary.

We did not observe direct adverse effects of PEBE. However, the risk of introducing a central venous catheter in a patient with shock and hemorrhagic diathesis should thoroughly be considered. Brandtzaeg et al. [14] reported the case of a patient who died after the retroperitoneal infusion of plasma because of the malposition of the femoral catheter. In our series, cannulation and perforation of the subclavian

Table 3. Presence of parameters with prognostic significance and outcome for patients who were treated conventionally and patients treated with early PEBE.

Parameter	Patients treated conventionally ($n = 10$)	Patients treated with early PEBE ($n = 13$)	P value
Age (y, median)	9.5	9	.90*
Preclinical disease period (h, median)	12	9	.53*
Delay in time to referral (h, median)	3	7.5	.33*
Referred patients (no.)	5/10	10/13	.37†
Fever (temperature, ≥40°C)	2/8	6/11	.41†
Leukocyte count in CSF, $\leq 100 \times 10^6$/L	6/7	7/12	.47†
Leukocyte count in peripheral blood, $\leq 10 \times 10^9$/L	6/10	7/13	1.00†
Platelet count, $\leq 100 \times 10^9$/L	5/10	3/13	.37†
Bicarbonate concentration, ≤15 mmol/L	7/10	7/12	.90†
Base excess concentration, ≤−8 mmol/L	7/10	6/12	.61†
Fibrinogen concentration, ≤1,500 mg/L	5/8	3/11	.29†
Mortality	6/10	1/13	.025†

NOTE. Early PEBE is that started within 30 hours after the first hospital admission.

* Wilcoxon's two-sample test.

† Continuity-adjusted χ^2 test.

vein led to fatal bleeding in patient 22. Still, in most patients with severe shock, rapid access to a central vein is necessary for diagnostic and therapeutic purposes. On the basis of these experiences, we advise that in these cases venous catheterization should be performed by an experienced physician, preferably into a compressible blood vessel.

Plasma endotoxin concentrations correlate with severity of the disease [19, 26]. We examined whether an accelerated elimination of endotoxin is responsible for the beneficial effect of PEBE. The elimination of endotoxin during the first 18 hours was approximately log-linear. In only four of seven patients, the elimination during the first PEBE session was increased compared with that during the period just before or after this session (figure 1). In this first 18 hours, the $t_{\frac{1}{2}}$ of endotoxin (± SEM) for individual patients ranged from 77 ± 3 minutes to 245 ± 27 minutes. The overall $t_{\frac{1}{2}}$ (± SEM), which was calculated for all patients, was 181 ± 18 minutes. This is in good accordance with the findings of Brandtzaeg et al. [20], who estimated a $t_{\frac{1}{2}}$ of 2 hours for 15 patients (of whom four were treated with PEBE) during the first 6 hours after admission and a $t_{\frac{1}{2}}$ of 6 hours during the following period. From these observations we conclude that an accelerated elimination of endotoxin is most likely not responsible for the improvement in the rate of survival.

We can only speculate about the beneficial mechanism of PEBE. An alternative suggestion is the removal of proinflammatory cytokines such as tumor necrosis factor and interleukin-1 (IL-1) [15]. This mechanism has been demonstrated in an experimental setting of *E. coli* sepsis in piglets, where PE was started during an early stage of the disease [27]. In our group, however, such a mechanism is not probable, because tumor necrosis factor and IL-1 are only detectable in the plasma during an early stage of the disease and disappear because of a short $t_{\frac{1}{2}}$ [28]. Another attractive hypothesis is that PEBE stimulates the production of antiinflammatory cytokines. The addition of IgG to the plasma (~1.2–2.0 g/kg in the first 24 hours) may stimulate the production of the IL-1 receptor antagonist (IL-1ra). Such a theory is in accordance with recent findings that IgG improves the survival rate among patients with septic shock [29], that IgG stimulates the production of IL-1ra, and that IL-1ra improves the rate of survival after lethal endotoxemia [30, 31]. In neonatal sepsis, BE is an accepted therapy [32]. Our results support its performance in children and adults with meningococcal sepsis. The beneficial mechanism of PEBE, however, is unclear, and the exact value of PEBE and its mode of action remain to be elucidated.

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References

1. Apicella MA. Neisseria meningitidis. In: Mandell GL, Douglas RG, Bennet JE, eds. Infectious diseases. New York: Wiley and Sons, 1985:1186–95.
2. Halstensen A, Pedersen SHJ, Haneberg B, Bjorvatn B, Solberg CO. Case fatality of meningococcal disease in Western Norway. Scand J Infect Dis 1987;19:35–42.
3. Cahalane SF, Waters M. Fulminant meningococcal septicaemia. A hospital experience. Lancet 1975;2:120–1.
4. McGehee WG, Rapaport SI, Hjort PF. Intravascular coagulation in fulminant meningococcemia. Ann Intern Med 1967;67:250–60.
5. Mercier J-C, Beaufils F, Hartmann J-F, Azéma D. Hemodynamic patterns of meningococcal shock in children. Crit Care Med 1988; 16:27–34.
6. Giraud T, Dhainaut J-F, Schremmer B, et al. Adult overwhelming meningococcal purpura. A study of 35 cases, 1977–1989. Arch Intern Med 1991;151:310–6.
7. Gårdlund B. Prognostic evaluation in meningococcal disease. A retrospective study of 115 cases. Intensive Care Med 1986;12:302–7.
8. Niklasson P-M, Lundbergh P, Strandell T. Prognostic factors in meningococcal disease. Scand J Infect Dis 1971;3:17–25.
9. Vik-Mo H, Lote K, Nordoy A. Disseminated intravascular coagulation in patients with meningococcal infection: laboratory diagnosis and prognostic factors. Scand J Infect Dis 1978;10:187–91.
10. Sinclair JF, Skeoch CH, Hallworth D. Prognosis of meningococcal septicaemia. Lancet 1987;2:38.
11. Girardin E, Grau GE, Dayer JM, Roux-Lombard P, The J5 Study Group, Lambert P-H. Tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. N Engl J Med 1988;319:397–400.
12. Thomson APJ, Sills JA, Hart CA. Validation of the Glasgow meningococcal septicemia prognostic score: a 10-year retrospective survey. Crit Care Med 1991;19:26–30.
13. Bjorvatn B, Bjertnaes L, Fadnes HO, et al. Meningococcal septicaemia treated with combined plasmapheresis and leucapheresis or with blood exchange. BMJ 1984;288:439–41.
14. Brandtzaeg P, Sirnes K, Folsland B, et al. Plasmapheresis in the treatment of severe meningococcal or pneumococcal septicaemia with DIC and fibrinolysis. Preliminary data on eight patients. Scand J Clin Lab Invest 1985;45(suppl 178):53–5.
15. Drapkin MS, Wisch JS, Gelfland JA, Cannon JG, Dinarello CA. Plasmapheresis for fulminant meningococcemia. Pediatr Infect Dis J 1989;8:399–400.
16. Westendorp RGJ, Brandt A, Thompson J, Dik H, Meinders AE. Experiences with plasma- and leucapheresis in meningococcal septicaemia. Intensive Care Med 1990;16(suppl 1):S102.
17. Østerud B. Meningococcal septicemia: the use of plasmapheresis or blood exchange and how to detect severe endotoxin induced white cell activation. Scand J Clin Lab Invest 1985;45(suppl 178):47–51.
18. Andersen BM. Mortality in meningococcal infections. Scand J Infect Dis 1978;10:277–82.
19. Scharfman WB, Tillotson JR, Taft EG, Wright E. Plasmapheresis for meningococcemia with disseminated intravascular coagulation. N Engl J Med 1979;300:1277.
20. Brandtzaeg P, Kierulf P, Gaustad P, et al. Plasma endotoxin as a predictor of multiple organ failure and death in systemic meningococcal disease. J Infect Dis 1989;159:195–204.
21. Natanson C, Hoffman WD, Danner RL, et al. A controlled trial of plasmapheresis (P) fails to improve outcome in an antibiotic treated

canine model of human septic shock (SS). Crit Care Med **1989**;17:S57.
22. Venkat-Raman G. Meningococcal septicaemia and meningitis: a rising tide. BMJ **1988**;296:1141–2.
23. Manios SG, Kanakoudi F, Maniati E. Fulminant meningococcemia. Heparin therapy and survival rate. Scand J Infect Dis **1971**;3:127–33.
24. Emperanza JI, Aldamiz-Echevarria L, Perez-Yarza EG, et al. Prognostic score in acute meningococcemia. Crit Care Med **1988**;16:168–9.
25. Dagbjartsson A, Ludvigsson P. Bacterial meningitis: diagnosis and initial antibiotic therapy. Pediatr Clin North Am **1987**;34:219–30.
26. Brandtzaeg P, Mollnes TE, Kierulf P. Complement activation and endotoxin levels in systemic meningococcal disease. J Infect Dis **1989**;160:58–65.
27. Busund R, Lindsetmo R-O, Rasmussen LT, Røkke O, Rekvig OP, Revhaug A. Tumor necrosis factor and interleukin 1 appearance in experimental Gram-negative septic shock. The effects of plasma exchange with albumin and plasma infusion. Arch Surg **1991**;126:591–7.
28. Waage A, Brandtzaeg P, Halstensen A, Kierulf P, Espevik T. The complex pattern of cytokines in serum from patients with meningococcal septic shock. Association between interleukin 6, interleukin 1, and fatal outcome. J Exp Med **1989**;169:333–8.
29. Schedel I, Dreikhausen U, Nentwig B, et al. Treatment of Gram-negative septic shock with an immunoglobulin preparation: a prospective, randomized clinical trial. Crit Care Med **1991**;19:1104–13.
30. Poutsiaka DD, Clark BD, Vannier E, Dinarello CA. Production of interleukin-1 receptor antagonist and interleukin-1β by peripheral blood mononuclear cells is differentially regulated. Blood **1991**; 78:1275–81.
31. Alexander HR, Doherty GM, Buresh CM, Venzon DJ, Norton JA. A recombinant human receptor antagonist to interleukin 1 improves survival after lethal endotoxemia in mice. J Exp Med **1991**; 173:1029–32.
32. Vain NE, Mazlumian JR, Swarner OW, Cha CC. Role of exchange transfusion in the treatment of severe septicemia. Pediatrics **1980**;66:693–7.