Intensive Care Med (2003) 29:564–569
DOI 10.1007/s00134-003-1676-4

ORIGINAL

Infectious diseases as a trigger in thrombotic microangiopathies in intensive care unit (ICU) patients?

Paul Coppo
Christophe Adrie
Elie Azoulay
Ghislaine Leleu
Eric Oksenhendler
Lionel Galicier
Jean Roger Le Gall
Annette Bussel
Benoît Schlemmer

Received: 24 May 2002
Accepted: 17 January 2003
Published online: 21 February 2003

P. Coppo · C. Adrie (✉) · E. Azoulay
G. Leleu · J. R. Le Gall · B. Schlemmer
Department of Critical Care Medicine,
Hôpital Saint-Louis
and University of Paris VII,
1 Rue Claude Vellefaux, 75010 Paris,
France
e-mail: christophe.adrie@wanadoo.fr
Tel.: +33-1-42499421
Fax: +33-1-42499430

E. Oksenhendler · L. Galicier
Department of Immuno-Hematology,
Hôpital Saint-Louis
and University of Paris VII,
1 Rue Claude Vellefaux, 75010 Paris,
France

A. Bussel
Department of Hemapheresis,
Hôpital Saint-Louis
and University of Paris VII,
1 Rue Claude Vellefaux, 75010 Paris,
France

Abstract *Objective:* Thrombotic microangiopathy (TMA) has been associated with a large number of underlying diseases. We conducted a descriptive, retrospective study including all TMA adult patients admitted to our ICU, with a particular interest in infectious episodes as a trigger of TMA. *Patients:* All adult patients (30) with a diagnosis of TMA admitted to the medical ICU at Saint-Louis Hospital (Paris, France) between 1992 and 1998 were retrospectively included. *Methods:* All patients with clinical and microbiological evidence of bacterial infection were treated with intravenous antibiotics. The specific treatment of TMA consisted in solvent/detergent-treated plasma administration by plasma exchange or high volume plasma infusion (30 ml/kg per day) in fractionated doses. *Results:* Among the 30 adult patients studied, TMA in 16 (53%) was associated with microbiologically documented infection. An acute infection was found in 8/9 patients with an HIV-related TMA, in 2/6 patients with a systemic lupus erythematosus (SLE)-related TMA and in 3/6 patients with TMA associated with other disorders. In three patients, an acute infectious disease was the only cause associated with the TMA. Four other patients had clinical manifestations suggesting an infection process but without bacteriological documentation. *Escherichia coli* was isolated in 7/16 cases and verotoxin was found in the stools of two other patients. All patients were treated with plasma administration and those with evidence of infection were systematically and intensively treated with antibiotics. Eventually 8 patients died (27%), 20 (67%) reached complete remission and 2 partial remission. *Conclusion:* Bacterial infections are commonly observed amongst TMA patients hospitalized in ICUs and may act as a trigger of this disease. Screening for infection is a requirement in patients with TMA, either idiopathic or associated with other conditions.

Keywords Thrombotic microangiopathy · Thrombotic thrombocytopenic purpura · Hemolytic uremic syndrome · Infection · Intensive care unit (ICU)

Introduction

The term thrombotic microangiopathy (TMA) encompasses the spectrum of classical thrombotic thrombocytopenic purpura (TTP) described first by Moschowitz [1] and hemolytic uremic syndrome (HUS) described three decades later by Gasser et al. [2]. TMA has been associated with various initiating factors, such as infectious diseases, drug intake, malignancies, connective tissue diseases and pregnancy [3, 4. It is characterized by microangiopathic hemolytic anemia with fragmented red cells (schistocytes), peripheral thrombocytopenia, fever,

neurological involvement and renal impairment. TMA (either TTP or HUS) is characterized by widening of the subendothelial space and intraluminal platelet thrombi [3]. The prognosis of TMA dramatically improved with plasma administration, either by infusion or plasma exchange, which remains the only well demonstrated effective therapy [5, 6]. However the superiority of plasma exchange compared to plasma infusion alone still remains a matter of debate [4, 6, 7, 8, 9, 10, 11, 12, 13].

Both endothelial cell injury and intravascular platelet aggregation have been implicated in the pathogenesis of TMA, leading to widespread platelet thrombi formation in the microcirculation, particularly in the brain and kidney, accounting for clinical symptoms [4, 10, 12]. Recently, Furlan and Tsaï [14, 15] have independently reported that TTP patients have a deficiency of von Willebrand factor-cleaving protease activity, either congenital or acquired, related to an inhibitory IgG autoantibody. Many case reports have described various infectious agents as responsible for inducing TMA, such as intra- or extra-cellular bacterial agents, viruses and fungal agents [16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30]. Recognition of these underlying diseases appears to be important in the management of TMA since they may be responsible for relapses or even treatment failure, and thus should be intensively diagnosed and treated [31].

We report on 30 patients with TMA managed in an intensive care unit (ICU). In most cases, TMA was associated with an infection, with a wide array of bacterial agents. We conducted a descriptive, retrospective study including all TMA adult patients admitted to our ICU, with a particular interest in infectious episodes as a trigger of TMA.

Patients and methods

Patients' characteristics

TMA diagnosis was retained, if at least four of the five following criteria were present [5]: (1) microangiopathic hemolytic anemia with schistocytes and negative Coombs test, (2) platelet count less than 100×10^9/l, (3) fever over 38°C, (4) renal and (5) central nervous system (CNS) involvement. The diagnosis was confirmed by the presence of intravascular hyaline thrombi in kidney biopsy samples when the diagnosis was controversial.

Infection was defined according to its clinical site, i.e. urinary tract infection (UTI), respiratory infection, ENT infection, gastrointestinal infection, meningoencephalitis, or skin and soft tissue infection. Routine tests on admission (blood and urine cultures) or subsequent tests were performed as indicated by clinical manifestations: stool culture, verotoxin (Shiga-like toxins using polymerase chain reaction) identification in stool, cerebrospinal fluid culture, bronchoscopy with protected brushing. During hospitalization in the ICU, physical examination and routine laboratory measurements were performed daily in all patients. Schistocytes were investigated every day for the first week and three times weekly thereafter. Both the Simplified Acute Physiology Score (SAPS II) [32] and the Logistic Organ Dysfunction system [33] were calculated on the first day in the ICU.

Treatment

All patients with clinical and microbiological evidence of bacterial infection were treated with intravenous antibiotics. The specific treatment of TMA consisted in solvent/detergent-treated plasma administration by plasma exchange or high volume plasma infusion (30 ml/kg per day) in fractionated doses [34]. Based on improvement of response criteria, these were reduced stepwise until plasma administration was withdrawn. Steroids were given to patients who did not present evidence of infection and aspirin when platelet count was more than 50×10^9/l. Vincristin and immunoglobulins were administered intravenously to patients with refractory TMA. The response criteria were improvement of neurological status, reduction of lactic dehydrogenase (LDH) levels and increase of platelets in the first 72 h as described by Patton et al. [35].

Results

Clinical and bacteriological findings

Thirty patients fulfilled the TMA criteria and were retrospectively included in the study over a 7-year period. In two patients, TMA was proved by biopsy. Nineteen patients were male and 11 were female, with a mean age of 43.3±15 years (mean ± SEM), a hemoglobin on admission of 8.1±0.3 g/dl, a platelet count of $40\pm8\times10^9$/l, a reticulocyte count of $18\pm17\times10^9$/l, a serum LDH of 2,515±652 U/l (12.5±3×N), a serum-free bilirubin of 39.7±8.6 µmol/l and a haptoglobin of 0.5±0.3 g/l. Schistocytes were observed on blood smear in 29 patients. Associated underlying diseases, clinical and biological data are reported in Table 1.

Sixteen patients (53%) presented TMA associated with a proved bacterial disease on admission. An acute infection was found in 8/9 patients with a HIV-associated TMA, in 2/6 patients with a systemic lupus erythematosus systemic lupus erythematosus (SLE)-associated TMA and in 3/6 patients with a TMA associated with another initiating factor, i.e. drug intake (4), acute leukemia (1) and postpartum (1). In three other patients, infectious disease was the only initiating factor associated with TMA. An infection was suspected clinically in four cases but without any bacteriological evidence (Table 2). In 7/16 patients, *Escherichia coli* was documented in lung and/or urine samples. It is noteworthy that *E. coli* was never found in stools. However, verotoxin was detected in the stools of two patients without direct identification of the causal pathogen. Finally, only two patients had idiopathic TMA without any underlying disease.

Organ dysfunction

On admission, mean SAPS II and LOD scores were 37.3±18.7 and 6.8±0.7, respectively. Twenty-seven patients presented central nervous system (CNS) involve-

Table 1 Clinical and biological characteristics on admission (*F* female, *M* male, *SAPS II* Simplified Acute Physiology Score II, *LOD* Logistic Organ Dysfunction, *Hb* hemoglobin, *LDH* lactic dehydrogenase, *HIV* human immunodeficiency virus, *SLE* systemic lupus erythematosus)

Patients	Associated diseases	Age (years)	Sex	SAPS II	LOD	Neurological involvement	Hb (g/dl)	Platelet count (10^9/l)	LDH (U/l)	Renal involvement
1	Infection	70	F	11	–	+	10.9	11	694	+
2	HIV disease Infection	33	M	10	7	+	9.9	52	661	–
3	SLE Infection	31	M	10	–	+	7.1	12	1,881	+
4	HIV disease Infection	43	M	79	7	+	4.1	38	3,640	+
5	None	71	F	44	–	–	8.2	21	3,710	+
6	Infection	66	M	16	10	+	7.2	6	1,812	+
7	Drug Infection	43	M	38	6	+	9.6	59	574	+
8	SLE Infection	66	F	51	6	+	4.9	4	697	+
9	HIV disease Infection	41	M	60	7	+	8.8	31	952	+
10	Infection	32	M	32	6	+	6.0	9	1,189	+
11	Drug	16	M	47	7	–	9.3	12	999	+
12	Infection	66	M	74	11	+	8.7	146	753	+
13	Infection	47	F	40	5	–	9.2	120	873	+
14	SLE	27	F	12	5	+	8.9	74	288	+
15	HIV disease Infection	32	M	49	3	+	7.1	50	606	+*
16	SLE	48	F	40	6	+	6.7	13	2,977	+
17	HIV disease	34	M	27	9	+	6.8	13	3,940	+
18	Post-partum	26	F	15	5	+	8.7	26	4,700	+
19	None	27	F	21	5	+	7.3	2	284	+
20	SLE	35	F	30	1	+	6.8	10	508	–
21	SLE	55	F	30	1	+	9.7	108	384	+
22	HIV disease Infection	43	M	16	5	+	4.9	7	1,244	+
23	Infection	49	M	41	3	+	10.6	8	3,229	+
24	HIV disease Infection	31	F	51	5	+	7.9	68	1,3680	+
25	HIV disease Infection	48	M	60	9	+	10	8	7,370	+
26	Drug Infection	68	M	47	14	–	8.4	73	1,590	+
27	Acute leukemia Infection	36	M	54	12	+	8.6	48	444	+
28	Infection	33	M	37	5	+	11.4	28	2,391	+
29	HIV disease Infection	44	M	27	–	+	8.8	143	–	+
30	Drug	39	M	50	–	+	7.9	9	–	+

*History of chronic renal failure

ment, ranging from headache (6/30) to seizure (9/30) or focal deficits (4/30) through confusion (12/30). The mean Glasgow coma score (GCS) was 11.6±0.9. Two patients received vasopressive drugs for septic shock-related hemodynamic failure. Seven patients required hemodialysis and 17 patients (57%) required mechanical ventilation, mostly because of CNS manifestations.

Treatment and outcome

Seventeen patients were managed with plasma infusion and 12 patients were treated with plasma exchange. Empirical antimicrobial therapy was initiated and then adapted to the microbiology results. A total of 20 patients (67%) reached complete remission. Two patients (7 and 15) achieved partial remission since platelet count and LDH remained abnormal after 6 months of follow-up. Two patients (3 and 22) relapsed 35 and 27 days after complete remission, respectively. They were treated with

Table 2 Characteristics and outcome of patients with a thrombotic microangiopathy (TMA) associated with an infectious disease (*CR* complete remission, *PR* partial remission, *PE* plasma exchange)

Patient	Infectious site(s)	Bacteria(s)	Outcome
1	Urine, blood	*Escherichia coli, Enterococcus faecalis*	Died
2	Lung	*Escherichia coli*	Died
3	Skin	*Staphylococcus aureus*	CR Relapsed by day 35, reached 2nd CR after 8 PEs
4	Digestive tract	*Verotoxin*	Died
6	Digestive tract	Not documented	CR
7	Lung	Not documented	PR
8	Blood	*Staphylococcus aureus, Candida albicans*	CR
9	Lung, blood, digestive tract	*Pseudomonas aeruginosa, Staphylococcus aureus, Clostridium difficile*	Died
10	Lung	*Staphylococcus aureus*	CR
12	Lung, blood, urine	*Staphylococcus aureus, Enterococcus faecalis*	CR
13	Digestive tract	Not documented	CR
15	Lung, blood	*Streptococcus pneumoniae*	PR
22	Digestive tract	*Verotoxin*	CR Relapsed by day 27, reached PR after 12 PEs
23	Gallbladder	Not documented	CR
24	Urine	*Escherichia coli*	CR
25	Lung	*Escherichia coli*	CR
26	Lung, blood	*Escherichia coli, Enterobacter fergussoni, Acinetobacter baumannii*	Died
27	Digestive tract, skin	*Escherichia coli, Torulopsis glabrata, Staphylococcus aureus, Streptococcus spp*	CR
28	Lung, bone marrow	*Mycobacterium tuberculosis*	CR
29	Blood, urine	*Escherichia coli, Enterococcus faecalis, Staphylococcus aureus*	Died

8 and 12 plasma exchanges, respectively. Patient 3 achieved a durable second remission. HIV-positive patient 22 was profoundly immuno-compromised and reached partial remission with persisting thrombocytopenia and increased LDH levels. TMA worsened in one patient (patient 16) after a good initial response to treatment with a concomitant nosocomial *E. coli* bacteremia from her urinary tract. Eventually plasma infusion and adapted antibiotics allowed for complete remission. In all survivors, a normalization of neurological status was observed. However, renal function remained unchanged and the clearance of serum creatinine did not improve either during hospitalization (46±7.9 ml/min at the admission to 50.1±5.9 ml/min at discharge) or during the follow-up ranging from 60 days to more than 6 years. Among the patients with infection-associated TMA, 12 (60%) reached complete remission, 2 reached partial remission and 6 (30%) died (Table 2). Among the latter, one (patient 29) died of hemodynamic failure related to sepsis while TMA was in complete remission.

Eight patients (27%) died despite treatment with a mean survival of 6.4±8.2 days. All four deceased HIV patients were profoundly immuno-compromised (CD4+ T-cell count: $0.053\pm0.05\times10^9$/l) and had proven bacterial infections without evidence for any other opportunistic pathogen co-infections. Death occurred in three patients with drug intake known to be associated with TMA and in one patient with bacterial infection and no other initiating factor.

Discussion

A large number of underlying processes have been associated with TMA, such as infections, drug intake, bone marrow transplantation, connective tissue diseases and pregnancy [4]. In the present study, we report that *E. coli* infections, but also other bacteria than Enterobacteriaceae species, are commonly associated with TMA amongst ICU patients whether or not they are related to an underlying disease. Fifty-three percent of the patients included had a proved infectious disease. *E. coli* or its toxin was isolated in nine patients. Bacterial agents isolated in our patients and previously reported as being associated with TMA were *Streptococcus pneumoniae* [16, 17] and *Mycobacterium tuberculosis* [18, 19]. To our knowledge, all other pathogens disclosed in our study have not been reported before. The clinical diagnosis of TMA mainly relies on non-specific signs and symptoms, and may be confusing in patients with severe sepsis, since this latter is responsible for hypoperfusion and organ failures that lead to CNS, renal and hematological dysfunction (i.e., thrombo-

penia and/or hemolysis) [19, 36]. Disclosure of schistocytes in blood smear, though not systematically present [10], histopathological lesions and response to plasma replacement are helpful in clarifying the diagnosis.

Since the first reports of HUS associated with bacteria of the family Enterobacteriaceae, such as *E. coli* (serotype O157/H7) and *Shigella dysenteriae* (serotype 1) [10, 11, 12], a large number of other infectious agents have been recognized as inducing TMA, such as *Streptococcus pneumoniae* [16, 17] and various other bacteria, such as *Mycobacterium tuberculosis* [18, 19], *Ehrlichia chaffensis* [21], *Borrelia burgdorferi* [22], *Legionella pneumophila* [23], *Bacteroides* bacteremia [24] and *Capnocytophaga canimorsus* [25, 26]. Furthermore, non-bacterial agents, such as herpes virus [27, 28], HIV [20] or other viruses [29] and fungal agents [30], have also been associated with TMA. The association between acute infection and TMA could either be related or not to an increase of susceptibility to infective agents or may be triggered by the infection.

The role of infectious agents in the pathogenesis and the occurrence of TMA has been implied by various experimental findings. Experiments on proliferating human umbilical vein endothelial cells strongly suggest that bacterial toxins like Shiga toxins are directly involved in endothelial cell injury [37] and in the release of the von Willebrand factor [4]. These mediators might be pivotal in the pathogenesis of vascular injury by up-regulating the expression of adhesion molecules and monocyte chemotactic protein, which results in neutrophil adhesion and activation with subsequent release of cytotoxic mediators [38]. Other investigators found that Fas transcripts were induced by plasma from patients with TTP or sporadic HUS in microvascular endothelial cells only in organs specifically involved in TTP, suggesting that these plasmas could mediate apoptosis [39]. Furthermore, large amounts of Fas-ligand are released in a sepsis model of cecal ligation and puncture in rats [40]. Damaged endothelial cells may result in the release of high levels of unusually large von Willebrand factor multimers, platelet activation and propagation of microvascular thrombosis, in patients with innate or acquired von Willebrand-cleaving metalloprotease deficiency [14, 15] or with a factor H deficiency [41].

Our study suggests that a careful search for infections and appropriate antimicrobial therapy should be automatically considered in infection-associated TMA. Like Creager et al. [31], we believe that occult bacterial infection may play a role in sustaining TTP and making it refractory to conventional treatment. However, this may depend on the infection site and, above all, on the bacteria involved, since antibiotic treatment of children with *E. Coli* O157:H7 gastrointestinal infections may indeed increase the risk of the hemolytic-uremic syndrome, which may be related to a release of Shiga-like toxin [42].

In conclusion, we observed that microbial agents other than classically described bacteria can potentially be responsible for severe TMA or may trigger this disease in patients who already have predisposing factors. Careful screening for infection and adapted antibacterial therapy are mandatory in patients with TMA, either idiopathic or associated with predisposing diseases.

References

1. Moschowitz E (1924) Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. Proc N Y Pathol Soc 24:21–24
2. Gasser C, Gautier E, Steck A, Siebenmann RE, Oechslin R (1955) Hämolytisch-urämische syndrome: bilaterale nierenrindennekrosen bei akuten erworbenen hämolytischen anämien. Schweiz Med Wochenschr 85:905–909
3. Remuzzi G (1987) HUS and TTP: variable expression of a single entity. Kidney Int 32:292–308
4. Ruggenenti P, Remuzzi G (1998) Pathophysiology and management of thrombotic microangiopathies. J Nephrol 11:300–310
5. Bell WR, Braine HG, Ness PM, Kichler TS (1991) Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. N Engl J Med 325:398–403
6. Rock GA (2001) Management of thrombotic thrombocytopathic purpura. Br J Haematol 109:496–507
7. Rock GA, Shumak KH, Buskard NA, Blanchette VS, Kelton JG, Nair RC, Spasoff RA and the Canadian Apheresis Group (1991). Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. N Engl J Med 325:393–397
8. Ruggenenti P, Galbusera M, Plata Cornejo R, Bellevita P, Remuzzi G (1993) Thrombotic thrombocytopenic purpura: evidence that infusion rather than plasma exchanges induces remission of the disease. Am J Kidney Dis 21:314–318
9. Novitzky N, Jacobs P, Rosenstrauch W (1994) The treatment of thrombotic thrombocytopenic purpura: plasma infusion or exchange? Br J Haematol 87:317–320
10. Remuzzi G, Ruggenenti P (1995) The hemolytic uremic syndrome. Kidney Int 47:2–19
11. Moake JL (1994). Haemolytic-uraemic syndrome: basic science. Lancet 343:393–396
12. Boyce TG, Swerdlow DL, Griffin P (1995) Escherichia coli O157-H7 and the hemolytic uremic syndrome. N Engl J Med 333:364–368
13. Fakhouri F, Vincent F, Legendre C (2000) Pathological and therapeutic distinction in HUS/TTP. Lancet 355:497
14. Tsai H-M, Lian EC-Y (1998) Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. N Engl J Med 339:1585–1594
15. Furlan M, Robles R, Galbusera M, Remuzzi G, Kyrle PA, Brenner B, Krause M, Scharrer V, Mittler U, Solenthaler M, Lämmle B (1998) Von Willebrand factor-cleaving protease in thrombotic thrombocytopenic purpura and the hemolytic-uremic syndrome. N Engl J Med 339:1578–1584

16. Moorthy B, Makker SP (1979) Hemolytic-uremic syndrome associated with pneumococcal sepsis. J Pediatr 95:558–559
17. Myers KA, Marrie TJ (1993) Thrombotic microangiopathy associated with streptococcus pneumoniae bacteremia: case report and review. Clin Infect Dis 17:1037–1040
18. Toscano V, Bontadini A, Falsone G, Conte R, Fois F, Fabiani A, Mariano VM, Rossi F (1995) Thrombotic thrombocytopenic purpura associated with primary tuberculosis. Infection 23:58–59
19. Pene F, Papo T, Brudy-Gulphe L, Cariou A, Pitte JC, Vinsonneau C (2001) Septic shock and thrombotic microangiopathy due to Mycobacterium tuberculosis in a non immunocompromised patient. Arch Intern Med 161:1347–1348
20. Hymes KB, Karpatkin S (1997) Human immunodeficiency virus infection and thrombotic microangiopathy. Semin Hematol 34:117–125
21. Marty AM, Dumler JS, Imes G, Brusman HP, Smrkovski LL, Frisman DM (1995) Ehrlichiosis mimicking thrombotic thrombocytopenic purpura. Case report and pathological correlation. Hum Pathol 26:920–925
22. Schröder St, Spyridopoulos I, König J, Jaschonek KG, Luft D, Seif FJ (1995) Thrombotic thrombocytopenic purpura (TTP) associated with a Borrelia burgdorferi infection. Am J Hematol 50:72–73
23. Riggs SA, Wray NP, Waddel CC, Rossen RD, Gyorkey F (1982) Thrombotic thrombo-cytopenic purpura complicating Legionnaires' disease. Arch Intern Med 142:2275–2280
24. Shalev O, Karni A, Kornberg A, Brezis M (1981) Thrombotic thrombocytopenic purpura associated with Bacteroides bacteremia. Arch Intern Med 141:692
25. Scarlett JD, Williamson HG, Dadson PJ, Fassett R, Peel MM (1991) A syndrome resembling thrombotic thrombocytopenic purpura associated with Capnocytophaga canimorsus septicemia. Am J Med 90:127–128
26. Finn M, Dale B, Isles C (1996) Beware of the dog! A syndrome resembling thrombotic thrombocytopenic purpura associated with Capnocytophaga canimorsus septicemia. Nephrol Dial Transplant 11:1839–1840
27. Satoh K, Takahashi H, Nagai K, Shibata A (1998) Thrombotic thrombocytopenic purpura and Herpes Zoster infection. Ann Intern Med 108:154–155
28. Jeejeebhoy FM, Zaltzman JS (1998) Thrombotic microangiopathy in association with cytomegalovirus infection in a renal transplant patient. Transplantation 65:1645–1648
29. Wasserstein A, Hill G, Goldfarb S, Goldberg M (1981) Recurrent thrombotic thrombocytopenic purpura after viral infection. Arch Intern Med 141:685–687
30. Miniero R, Nesi F, Vai S (1997) Cryptococcal meningitis following a thrombotic microangiopathy in an unrelated donor bone marrow transplant recipient. Pediat Hematol Oncol 14:469–474
31. Creager AJ, Brecher ME, Bandarenko N (1998) Thrombotic thrombocytopenic purpura that is refractory to therapeutic plasma exchange in two patients with occult infection. Transfusion 38:419–423
32. Le Gall JR, Lemeshow S, Saulnier F (1993) A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study. JAMA 270:2957–2963
33. Le Gall JR, Klar J, Lemeshow S, Saulnier F, Alberti C, Artigas A, Teres D for the ICU scoring group (1996) The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. JAMA 276:802–810
34. Coppo P, Bussel A, Charrier S, Adrie C, Galicier L, Boulanger E, Veyrandier A, Leblanc T, Alberti C, Azoulay E, Le Gall JR, Schlemmer B (2003) High dose plasma infusion versus plasma exchange as early treatment of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome. Medicine 82:27–38
35. Patton JF, KR Manning, Case D, Owen J (1994) Serum lactate deshydrogenase and platelet count predict survival in thrombotic thrombocytopenic purpura. Am J Hematol 47:94–99
36. Light BR (1992) Sepsis syndrome. In: Hall JB, Schmidt GA, Wood LD (eds) Principles of critical care. McGraw-Hill, New York, pp 645–655
37. Obrig TG, Del Vecchio PJ, Brown JE, Moran TP, Rowland BM, Judge TK, Rothman SW (1988) Direct cytotoxic action of Shiga toxin on human vascular endothelial cells. Infect Immun 56:2373–2378
38. Keusch GT, Acheson DWK (1997) Thrombotic thrombocytopenic purpura associated with Shiga toxins. Semin Hematol 34:106–116
39. Laurence J, Mitra D, Steiner M, Staiano-Coico L, Jaffe E (1996) Plasma from patients with idiopathic and human immunodeficiency virus-associated thrombotic thrombocytopenic purpura induces apoptosis in microvascular endothelial cells. Blood 87:3245–3246
40. Tannahill CL, Fukuzuka K, Marum T, Abouhamze Z, MacKay SL, Copeland EM 3rd, Moldawer LL (1999) Discordant tumor necrosis factor-alpha superfamily gene expression in bacterial and endotoxemic shock. Surgery 126:349–357
41. Noris M, Ruggenenti P, Pena A, Orisio S, Caprioli J, Skerka C, Vasile B, Zipfel PF, Remuzzi G (1999) Hypocomplementemia discloses predisposition to hemolytic uremic syndrome and thrombotic thrombocytopenic purpura: role of factor H abnormalities. J Am Soc Nephrol 10:281–293
42. Wong CS, Jelacic SJ, Habeeb RL, Watkins SL, Tarr PI (2000) The risk of the hemolytic-uremic syndrome after antibiotic treatment of Escherichia coli O157:H7 infections. N Engl J Med 342:1930–1936