is not transfused; this type of DIC is called the massive bleeding or consumptive type of DIC. This form of DIC is observed in patients who exhibit major bleeding after major surgery or in those with obstetric diseases.

When both vectors are weak, there are almost no clinical symptoms, although abnormalities in clinical laboratory tests are observed; this type of DIC is called the non-symptomatic type of DIC or pre-DIC [14,15]. In a retrospective study [15], the treatment of pre-DIC was reported to be effective. The diagnosis and treatment of the four types of DIC differ [3]. Furthermore, the diagnosis and treatment of DIC is complicated by the fact that the types of DIC may shift or change. Patients with DIC caused by sepsis (organ failure type), hematological malignancy, or obstetrics (bleeding type) can be successfully treated for DIC, whereas DIC associated with solid cancers may not respond to standard treatments [16]. As DIC associated with solid cancers differs from the above four types of DIC, it should be analyzed separately.

Diagnosis of DIC

Scoring system

Various underlying clinical conditions can have an effect on the laboratory parameters that are usually obtained to diagnose DIC, such as global coagulation tests, the platelet count, prothrombin time (PT), and the fibrinogen, fibrinogen, and fibrin degradation products (FDPs). In order to facilitate the diagnostic process for detecting DIC, the use of a scoring system is recommended by each of the four different guidelines [3-6]. Three different diagnostic criteria incorporating similar global coagulation tests have been established by the ISTH/SSC [1], Japanese Ministry Health, Labour and Welfare (JMHLW) [17], and Japanese Association of Acute Medicine (JAAM) [18]. The JMHLW score is well correlated with the severity of DIC and can be used to predict the outcome of the disease [14]. The ISTH overt DIC score is useful and specific for diagnosing DIC due to infective and non-infective etiologies [13,19]. The JAAM score is sensitive for detecting septic DIC and is correlated with the ISTH and JMHLW scores and disease outcome [13,18]. A prospective study in Japan reported no significant differences in the odds ratio for predicting DIC outcomes among these three diagnostic criteria [20], suggesting that the identification of molecular hemostatic markers and changes of global coagulation tests is required in addition to the application of scoring systems. The use of a combination of tests repeated over time in patients with suspected DIC can be used to diagnose the disorder with reasonable certainty in most cases [21-23]. A template for a non-overt-DIC scoring system, including global coagulation tests, changes in global coagulation tests as well as hemostatic molecular markers, has been proposed [1,24,25].

The bleeding type of DIC can be easily diagnosed using the ISTH overt-DIC [1] and JMHLW [17] criteria, while the organ failure type of DIC is diagnosed according to the JAAM diagnostic criteria [18]. The massive bleeding (consumptive) type of DIC can be diagnosed using any of the three diagnostic criteria [1,17,18]; however, it is difficult to diagnose the non-symptomatic type of DIC using these criteria. The use of hemostatic molecular markers is required to diagnose the non-symptomatic type of DIC.

Laboratory tests

Global coagulation tests provide important evidence regarding the degree of coagulation factor activation and consumption. Although the PT is prolonged in approximately 50% of patients with DIC at some point during their clinical course [21], abnormalities are often observed in patients with liver disease or vitamin K deficiency. A reduction in the platelet count or clear downward trend in subsequent measurements is a sensitive sign of DIC [3], although this pattern is also observed in patients with bone marrow disorders. A reduced fibrinogen level is a valuable indicator regarding a diagnosis of DIC due to leukemia or obstetric diseases; however, it is not observed in most septic DIC patients [3]. Elevated fibrin-related markers (FRMs), such as FDP [26], D-dimer [27], or soluble fibrin (SF), reflect fibrin formation. SF [28] assays offer theoretical advantages in detecting DIC, more closely reflecting the effects of thrombin on fibrinogen, although the half-life is short. It is important to consider that many conditions, such as trauma, recent surgery, bleeding, or venous thromboembolism (VTE), are associated with elevated FRMs. Reductions in the levels of natural anticoagulants, such as antithrombin (AT) and protein C, are common in patients with DIC. Although measuring the AT activity is useful for achieving the full efficacy of heparin [29], this parameter cannot be quickly and easily measured in all hospitals. These activities are correlated with the liver function and/or concentration of albumin. A reduced ADAMTS13 (a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13) activity and elevated soluble thrombomodulin (TM), PAI-I, and von Willebrand factor propeptide levels are often observed in patients with DIC and have been shown to have prognostic significance [30-32]. The biphasic waveform of the activated partial thromboplastin time (APTT) has been shown to be associated with DIC and appears to have a positive predictive value for the disease [33,34]. Although many attractive markers for DIC have been reported, no single marker can be used to diagnose DIC alone (Table 2). Therefore, the above four guidelines [3-6] recommend that DIC could not be diagnosed according to the level of a single marker but rather based on the combination of laboratory markers. Among the

Table 2 Laboratory tests for DIC

	Abnormality in DIC	Other cause for the abnormality	Adequate type of DIC
PT	Prolongation	Liver dysfunction, vitamin K deficiency	OF, BL, MB
FDP, D-dimer	Elevation	Venous thromboembolism, operation	BL, NS, OF
Fibrinogen	Reduction	Liver dysfunction	BL, MB
Platelet count	Reduction	Bone marrow disorders	OF, MB, BL, NS
AT/PC	Reduction	Liver dysfunction, capillary leak syndrome	OF
SF/TAT	Elevation	Venous thromboembolism, operation	OF, NS, BL, MS
TM	Elevation	Renal dysfunction, organ failure	OF
VWFpp, PAI-I	Elevation	Organ failure	OF
ADATMTS13	Reduction	Liver dysfunction, thrombotic microangiopathy	OF
APTT	Biphasic waveform	Infection	OF
PPIC	Elevation	Venous thromboembolism, operation	BL, MB

PT, prothrombin time; FDP, fibrinogen and fibrin degradation products; SF, soluble fibrin; AT, antithrombin; PC, protein C; TAT, thrombin AT complex; VWFpp, von Willebrand factor propeptide; PAI-I, plasminogen activator inhibitor-I; APTT, activated partial thromboplastin time; PPIC, plasmin-plasmin inhibitor complex; OF, organ failure type of DIC; BL, bleeding type of DIC; MB, massive bleeding type of DIC; NS, non-symptomatic type of DIC.

four types of DIC, PT, fibrinogen, and platelets are important parameters for diagnosing the massive bleeding type of DIC, while fibrinogen, FDP, and plasmin-plasmin inhibitor complex (PPIC) are important for detecting the bleeding type of DIC. Meanwhile, platelets, PT, and AT are important for diagnosing the organ failure type of DICand hemostatic molecular markers, such as SF and the thrombin-AT complex, are important for diagnosing the non-symptomatic type of DIC.

Treatment of DIC

Treatment of the underlying disease

The cornerstone of DIC treatment is providing treatment for the underlying disorders, such as the administration of antibiotics or surgical drainage in patients with infectious diseases and anticancer drugs or surgery in patients with malignant diseases. All four guidelines [3-6] agree on this point, although there is no high-quality evidence for the efficacy of treating the underlying disorder in DIC patients. DIC spontaneously resolves in many cases when the underlying disorder is properly managed and improved. However, some cases require additional supportive treatment specifically aimed at abnormalities in the coagulation system. A randomized controlled trial (RCT) of the use of all-trans retinoic acid (ATRA) compared with conventional chemotherapy in patients with APL showed that the mortality rate was significantly lower in the ATRA group [35]. ATRA exerts differential effects on APL progression, as well as anticoagulant and antifibrinolytic effects [36]. Similarly, several RCTs of the treatment of sepsis [37-42] and DIC [43] have shown parallel improvements in coagulation derangement and DIC, although the data have not always been concordant. Treating the underlying disorder is first required in patients with bleeding, organ failure, and non-symptomatic types of DIC, while blood transfusions are needed in patients with the massive bleeding type of DIC (Table 3).

Blood transfusion

Markedly low levels of platelets and coagulation factors, particularly fibrinogen, may increase the risk of bleeding. The above four guidelines [3-6] recommended the administration of platelet concentrate (PC) and fresh frozen plasma (FFP) in DIC patients with active bleeding or those at high risk of bleeding requiring invasive procedures, without high-quality evidence. The threshold for transfusing platelets depends on the clinical state of the DIC patient. In general, PC is administered in DIC patients with active bleeding and a platelet count of $\leqq 50 \times 10^9$/l. A much lower threshold of 10 to 20×10^9/l is adopted in non-bleeding patients who develop DIC after undergoing chemotherapy. PC may be administered at higher levels in patients perceived to be at high risk of bleeding based on other clinical or laboratory features [44]. The transfusion of PC or FFP is usually performed in patients with the massive bleeding or bleeding types

Table 3 Treatment of DIC in four types of DIC

Treatment	Non-symptomatic type	Organ failure type	Bleeding type	Massive bleeding type
Underlying conditions	R	R	R	
Blood transfusion			R	R
Heparin	R		NR	NR
Anti-Xa			NR	NR
Synthetic protease inhibitor			R	R
Natural protease inhibitor		R		NR
Antifibrinolytic treatment	NR	NR	R	R

R, recommended; NR, not recommended.

of DIC. It is necessary to use large volumes of plasma in order to correct coagulation defects associated with a prolonged APTT or PT (greater than 1.5 times the normal value) or decreased fibrinogen level (less than 1.5 g/dl). An initial dose of 15 ml/kg of FFP is clinically recommended and usually administered. As the consequences of volume overload must be considered in this context, smaller volumes of prothrombin complex concentrate may be useful in this setting. As specific deficiencies in fibrinogen associated with the massive bleeding type of DIC can be corrected with the administration of purified fibrinogen concentrates or cryoprecipitate, three of the guidelines recommended these treatments (Table 3). The response to blood component therapy should be monitored both clinically and with repeated assessments of the platelet count and coagulation parameters following the administration of these components. The efficacy and safety of recombinant factor VIIa in DIC patients with life-threatening bleeding are unknown, and this treatment should be used with caution or as part of a clinical trial.

Heparin

Although the administration of anticoagulant treatment is a rational approach based on the notion that DIC is characterized by extensive activation of coagulation, there are several differences in the recommendations for the use of heparin in DIC patients between the four guidelines (Table 1) [3-6]. Therapeutic doses of heparin should be considered in cases of DIC in which thrombosis predominates. A small RCT showed that low molecular weight heparin (LMWH) is superior to unfractionated heparin (UFH) for treating DIC [45], suggesting that the use of LMWH is preferred to that of UFH in these cases. The level of inhibition achieved with LMWH is higher for activated coagulation factor Xa (Xa) than for thrombin. Patients with DIC are at high risk of VTE events, and the administration of VTE prophylaxis using UFH, LMWH, and/or mechanical methods has become the standard of care in patients with DIC [46,47]. Although experimental studies have shown that heparin can at least partly inhibit the activation of coagulation in the setting of DIC [48], there are no RCTs demonstrating that the use of heparin in patients with DIC results in improvements in clinically relevant outcomes. A recent large trial of patients with severe sepsis showed a non-significant benefit of low-dose heparin on the 28-day mortality and underscored the importance of not discontinuing heparin treatment in patients with DIC and abnormal coagulation parameters [29]. Meanwhile, the 28-day mortality is lower in placebo groups treated with heparin than in placebo groups without heparin according to subclass analyses [49] of RCT of severe sepsis [37,38,42]. Although it is not easy to quickly measure the AT level in all hospitals in order to decide whether to administer urgent heparin treatment, measuring this parameter is useful for achieving the full efficacy of heparin. The administration of heparin is not recommended in patients with bleeding or massive bleeding type of DIC due to the increased risk of bleeding, although it is recommended in those with the non-symptomatic type of DIC in order to prevent the onset of deep vein thrombosis (DVT) (Table 3).

Anti-Xa agents

Both Fondaparinux® and Danaparoid sodium® activate AT specifically to inhibit Xa. Treatment with Fondaparinux® is recommended for the prophylaxis of DVT after orthopedic surgery; however, there is little evidence to support its use in critically ill patients and those with other type of DIC. Danaparoid sodium® is used to treat DIC in Japan, although no RCTs have shown any reductions in mortality or the rate of resolution of DIC. There is significant evidence for the use of these drugs as prophylaxis for DVT [50,51]; however, there is little evidence for the use of these agents in patients with DIC, and they are not recommended in those with the bleeding or massive bleeding type of DIC (Table 3). These drugs are also not recommended in patients with renal failure.

Synthetic protease inhibitors

Synthetic protease inhibitors, such as Gabexate mesilate® and nafamostat®, exhibit multiple-functions, including antagonistic effects on the kinin/kallikrein system, fibrinolysis, complement system, and coagulation system. Gabexate mesilate® and nafamostat® have been frequently used and evaluated in Japan [13,52,53]; however, there are no RCTs showing any reductions in mortality or improvements in the rate of resolution of DIC. As these drugs have mild anticoagulant and antifibrinolytic effects, they are often used in patients with the bleeding, massive bleeding, and non-symptomatic types of DIC (Table 3).

Natural protease inhibitor

The use of agents capable of restoring dysfunctional anticoagulant pathways in patients with DIC has been studied extensively. Although there are many RCTs of clinically ill patients, almost all RCTs have been carried out in patients with sepsis, with few RCTs of patients with DIC, suggesting that BCSH and SISET determined their recommendations for DIC treatment based on studies of sepsis, not DIC.

AT and the heparin/heparinoid complex primarily inhibits Xa and thrombin, while the APC/TM system inhibits thrombin, FVa, and FVIIIa (Figure 2). Each of the four guidelines [3-6] provides different recommendations regarding the use of anticoagulant factor concentrates (Table 1). A large-scale multicenter RCT directly assessing the effects of AT concentrate on mortality in

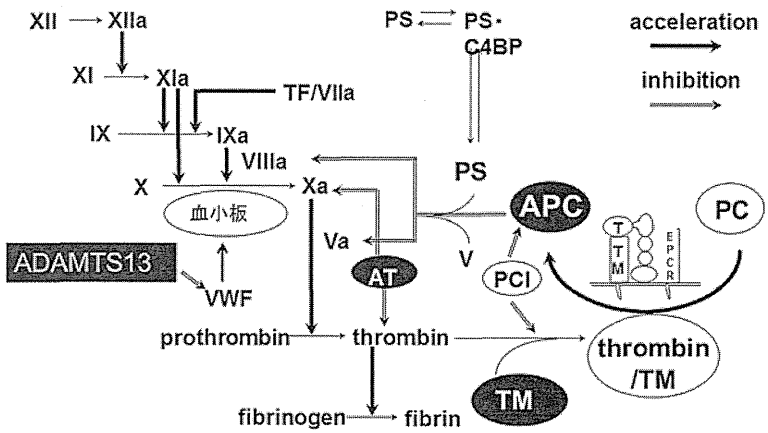

Figure 2 Regulation of the coagulation system.

patients with severe sepsis showed no significant reductions in those treated with AT concentrate [37]. Interestingly, the subgroup of patients with DIC and who did not receive heparin showed a remarkable survival benefit [54]; however, this finding requires prospective validation. In one prospective multicenter survey, the efficacy of AT was higher in the 3,000 units/day group than in the 1,500 units/day group [55].

The clinical efficacy of recombinant human activated protein C (rhAPC) in patients with severe sepsis was demonstrated in a large RCT [38], although a prospective trial of septic patients with relatively low disease severity did not show any benefits of rhAPC therapy [39]. The withdrawal of rhAPC from sepsis treatment regimens was proposed after an RCT of septic shock failed to show any benefits [40]. Meanwhile, treatment with plasma-derived APC improved outcomes in a small RCT [56] in Japan; however, the drug is not approved for the treatment of DIC. There are no useful RCTs of the administration of protein C concentrate to treat sepsis or DIC.

One RCT comparing treatment with rhTM with that of UFH [43] showed that rhTM therapy significantly increased the rate of resolution of DIC, although mortality was not significantly decreased. In another study of DIC, treatment with rhTM relatively reduced mortality and significantly reduced the severity of organ failure compared to a placebo [57]. Another RCT of severe sepsis showed that the administration of rhTM tended to improve mortality [41].

The administration of AT, rhTM, or APC may be considered in DIC patients. Further prospective evidence from RCTs confirming a benefit is required [6]. Treatment with AT and rhTM is recommended in patients with the organ failure type of DIC (Table 3).

Antifibrinolytic treatment

Antifibrinolytic agents are effective in treating bleeding, although the use of these drugs in patients with the organ failure or non-symptomatic type of DIC is generally not recommended [58]. An exception may be made in those with the bleeding or major bleeding type of DIC. The four guidelines [3-6] exhibit some differences in these recommendations (Table 1). One study of APL demonstrated a beneficial effect of antifibrinolytic agents in this situation [59]; however, cases complicated with severe thrombosis due to the combined use of ATRA and tranexamic acid have been documented [60]. A recent RCT [61] showed that treatment with tranexamic acid significantly reduces the mortality of patients with trauma. The administration of antifibrinolytic agents in these cases must occur in the early period of management before the levels of PAI-1 and other endogenous antifibrinolytics become elevated.

Conclusions

In conclusion, DIC is categorized into bleeding, organ failure, massive bleeding, and non-symptomatic types. The diagnosis and treatment of DIC should be carried out in accordance with the type of DIC based on the four guidelines on DIC.

Abbreviations

ADAMTS13: a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13; APL: acute promyelocytic leukemia; APTT: activated partial thromboplastin time; AT: antithrombin; ATRA: all-trans retinoic acid; BCSH: British Committee for Standards in Haematology; DIC: disseminated intravascular coagulation; FDP: fibrinogen and fibrin degradation products; FFP: fresh frozen plasma; FRMs: fibrin-related markers; HMGB-1: high mobility group box 1; ISTH: International Society of Thrombosis and Haemostasis; JAAM: Japanese Association of Acute Medicine; JMHLW: Japanese Ministry Health, Labour and Welfare; JSTH: Japanese Society of Thrombosis and Hemostasis; LMWH: low molecular weight heparin; LPS: lipopolysaccharide; NETs: neutrophil extracellular traps; PAI-I: plasminogen activator inhibitor I; PC: platelet concentrate; PT: prothrombin time; RCT: randomized controlled trial; rh: recombinant human activated protein C; SF: soluble fibrin; SISET: Italian Society for Thrombosis and Haemostasis; SSC: Scientific and Standardization Committee; TFPI: tissue factor pathway inhibitor; TM: thrombomodulin; UFH: unfractionated heparin; VTE: venous thromboembolism.

Competing interests
None of the authors disclose any financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

Authors' contributions
HW mainly contributed to write this paper. TM and YY mainly contributed to review references. All of authors discussed for this review. All authors read and approved the final manuscript.

Acknowledgements
This study was supported in part by research grants from the Japanese Ministry of Health, Labour and Welfare and the Japanese Ministry of Education, Science, Sports and Culture.

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Received: 18 December 2013 Accepted: 10 February 2014
Published: 20 February 2014

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doi:10.1186/2052-0492-2-15
Cite this article as: Wada *et al.*: Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. *Journal of Intensive Care* 2014 2:15.

Clinica Chimica Acta 436 (2014) 130–134

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Invited critical review

Disseminated intravascular coagulation: Testing and diagnosis

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ARTICLE INFO

Article history:
Received 11 March 2014
Received in revised form 19 April 2014
Accepted 22 April 2014
Available online 30 April 2014

Keywords:
DIC
Diagnostic criteria
Mortality
Hemostatic abnormality
Treatment

ABSTRACT

Abnormalities of the hemostatic system in patients with DIC result from the sum of vectors for hypercoagulation and hyperfibrinolysis. DIC is classified into hyperfibrinolysis, hypercoagulation, massive bleeding or nonsymptomatic types according to the balance of the two vectors. Both the antithrombin (AT) and protein C (PC) levels are significantly low in patients with septic DIC, and reduced amounts of AT and PC result in the lack of inhibition of thrombin and activated FVIII, respectively. Thrombin activates FVIII, while activated FVIII accelerates the coagulation pathway to generate thrombin; thus activation of the coagulation system persists.
Three sets of diagnostic criteria have been established by the Japanese Ministry of Health, Labour and Welfare, International Society of Thrombosis and Haemostasis and Japanese Association for Acute Medicine, respectively. Although these three diagnostic criteria score hemostatic abnormalities using similar global coagulation tests, the sensitivity and/or specificity for death differ. Treatment with AT or activated PC may not improve the outcomes of patients with sepsis at the early stage, although they may improve the outcomes in those with DIC.
Therefore, new diagnostic criteria for determining the appropriate time to initiate anticoagulant treatment are required.

Contents

1. Introduction

Disseminated intravascular coagulation (DIC) was first reported in patients with gynecological disease, leukemia and solid cancer [1,2], and the concept of DIC was established from these reports. Severe bleeding and/or consumptive coagulopathy are observed in most cases, and it is necessary to detect microthrombi in DIC patients with bleeding prior to administering heparin before the establishment of the concept of DIC. Although several groups have proposed various diagnostic criteria for DIC [3–6], the treatment of a pathological state as DIC does not require antithrombotic or antifibrinolytic therapy in cases in which the patient is considered to have coagulopathy due to an underlying disease. Additionally, although previous criteria have been applied in research, they are difficult to implement in clinical practice. In 1979, the Japanese Ministry of Health, Labour and Welfare (JMHLW) established diagnostic criteria for DIC involving the evaluation of global coagulation tests, underlying diseases and clinical symptoms [7]. Therefore, most Japanese physicians have been able to easily diagnose DIC since 1979. In contrast, most physicians in North America and Europe experienced difficulty in diagnosing DIC before 2001. In 2001, the International Society on Thrombosis and

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http://dx.doi.org/10.1016/j.cca.2014.04.020
0009-8981/

Haemostasis (ISTH) published a definition of DIC and overt-DIC diagnostic criteria involving the use of global coagulation tests based on the JMHLW criteria [8]. Subsequently, diagnosing DIC in North America and Europe has become easier, and these diagnostic criteria have since been used and analyzed in many clinical studies. Importantly, the ISTH guidance recommends that the diagnosis of DIC is made based on the above scoring system not with a single test [9].

Many clinical trials have been conducted using antithrombin (AT) [10], recombinant human activated protein C (rhAPC) [11,12] and rh tissue factor pathway inhibitor (rhTFPI) [13] in cases of severe sepsis, as well as plasma-derived APC [14] and rh-thrombomodulin (rhTM) [15] in subjects with DIC. Although treatment with AT, rhTFPI and rhAPC has not been shown to improve mortality, these drugs reduce the hemostatic abnormalities. Many patients with severe sepsis were treated with rhAPC before 2012, primarily in North America and Europe, while those with septic DIC are treated with AT or rhTM in Japan. Therefore, the ISTH guidance proposes that the administration of AT, rhTM or ahAPC might be considered in DIC patients [9].

2. Definition

The definition of DIC differs depending on whether the term is used by clinicians, laboratory technologists, research scientists, administrators or businessmen in the private sector and can also vary depending on social infrastructure, geographical location, economic conditions, the level of health care, the history of research on DIC, etc [16]. DIC may eventually be considered a condition that can be effectively treated with anticoagulant therapy, rather than a disease with a poor prognosis. The expression "death is coming (DIC)" is used to reflect the severity of DIC as a disease with a poor outcome. The earliest definition and concept of DIC required evidence of the presence of microthrombi and emphasized the tendency for prominent hemorrhage caused by consumptive coagulopathy resulting from the formation of multiple microthrombi [1]. It is difficult to directly prove the presence of microthrombi in most patients with DIC; therefore, the results of clinical laboratory tests of fibrin-related markers are used instead. In addition, symptoms of organ failure due to microthrombosis are now considered to be more important than those deriving from hemorrhagic conditions. The concept of disseminated intravascular fibrin formation was previously proposed, and researchers have attempted to diagnose DIC based on increases in the level of soluble fibrin (SF) [17,18]. The ISTH confirmed the importance of fibrin-related products in patients with DIC and proposed a definition of DIC as follows; "DIC is an acquired syndrome characterized by the intravascular activation of coagulation with the loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction [8]."

2.1. Pathophysiology of DIC

Abnormalities of the hemostatic system in patients with DIC result from the sum of vectors for hypercoagulation and hyperfibrinolysis (Fig. 1). When the vector for hyperfibrinolysis is remarkable and dominant, bleeding is the primary symptom; this type is called the bleeding type or hyperfibrinolysis type of DIC. This form of DIC is often observed in patients with leukemia, such as acute promyelocytic leukemia (APL), obstetric diseases or aortic aneurysms [1,2]. On the other hand, when the vector for hypercoagulation is remarkable and dominant, organ failure due to microthrombi is the main symptom; this type of DIC is called the organ failure type, hypercoagulation type or hypofibrinolysis type of DIC. This form of DIC is often observed in patients with infection, paticularly sepsis [19]. An increase in the level of plasminogen activator inhibitor I (PAI-I) induced by marked increased levels of cytokines [20, 21] and lipopolysaccharide (LPS) [1,2] in the blood has been reported to be a cause of hypofibrinolysis. Moreover, neutrophil extracellular traps (NETs) [22], which release DNA with histone, neutrophil elastase and cathepsin G in order to trap and kill pathogens, are present in patients with sepsis. Histones promote the apoptosis of vascular endothelial cells and platelet aggregation [23], while neutrophil elastase and cathepsin G decompose tissue factor pathway inhibitor (TFPI) to promote thrombus formation [24]. Moreover, high mobility group box 1 (HMGB-1) [25] is emitted from injured and dead cells in order to enhance the inflammatory reaction. When both vectors for hypercoagulation and

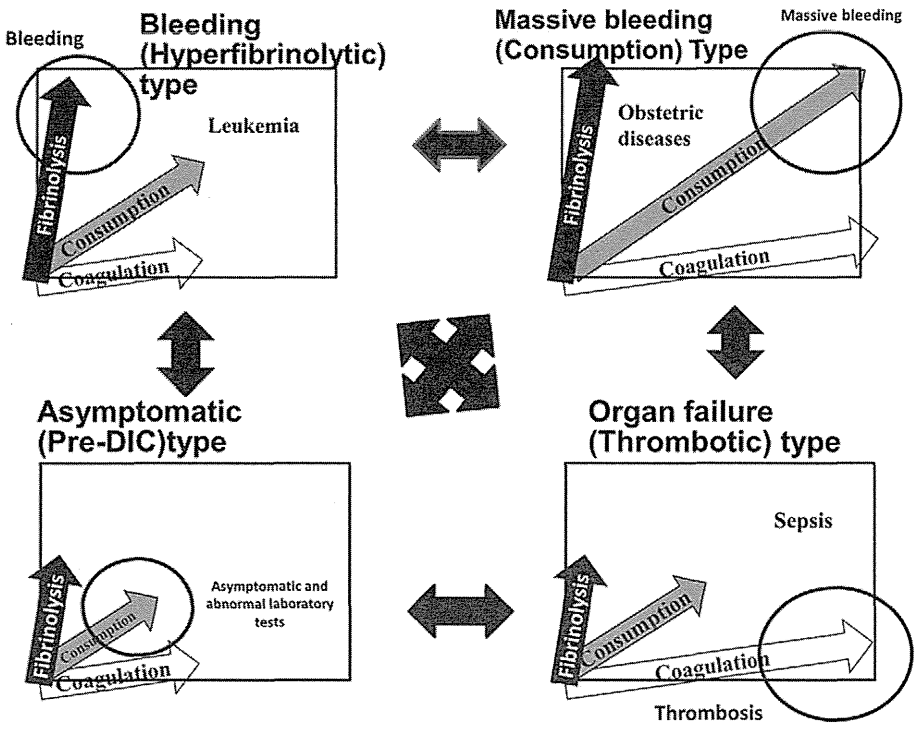

Fig. 1. Four types of DIC.

hyperfibrinolysis are remarkable and strong, major bleeding occurs, followed by death, if a sufficient amount of blood is not transfused; this type of DIC is called the massive bleeding or consumptive type of DIC. This form of DIC is observed in patients who exhibit marked consumption of coagulation factors and major bleeding after major surgery or in those with obstetric diseases. When both vectors are not markedly strong, there are almost no clinical symptoms, although abnormalities in clinical laboratory tests are observed; this type of DIC is called the non-symptomatic type of DIC or pre-DIC [26,27]. In a retrospective study [28], the treatment of pre-DIC was reported to be effective. The diagnosis and treatment of the four types of DIC differ [29]. Furthermore, the diagnosis and treatment of DIC are complicated by the fact that the types of DIC may shift or change (**Fig.** 1). Patients with DIC caused by sepsis (organ failure type), hematological malignancy or obstetrics (bleeding type) can be successfully treated for DIC, whereas DIC associated with solid cancers may not respond to standard treatments [30,31]. As the outcome of DIC associated with solid cancers differs from DIC resulting from infection, leukemia or obstetrical causes, it should be analyzed separately.

The causes of DIC in patients with leukemia (bleeding type) are considered to include hyper-expression or massive release of tissue factor (TF), plasminogen activator and annexin II [32-35] from leukemic cells. A large volume of TF and PA strongly activates extrinsic pathway and fibrinolytic system, thus causing bleeding and thrombosis. In such cases, antithrombin (AT) and protein C cannot sufficiently inhibit the activation of the extrinsic pathway (Fig. 2A). In contrast, the release of TF from activated leukocytes is another cause of DIC in patients with sepsis [36,37]. In particular, in septic patients, lipopolysaccharides (LPS) derived from Gram-negative bacteria and peptidoglycans derived from Gram-positive bacteria activate toll-like receptors (TLRs) [38,39] and CD14 in macrophages. The activation of TLR and CD14 in turn stimulates nuclear factor-kappa

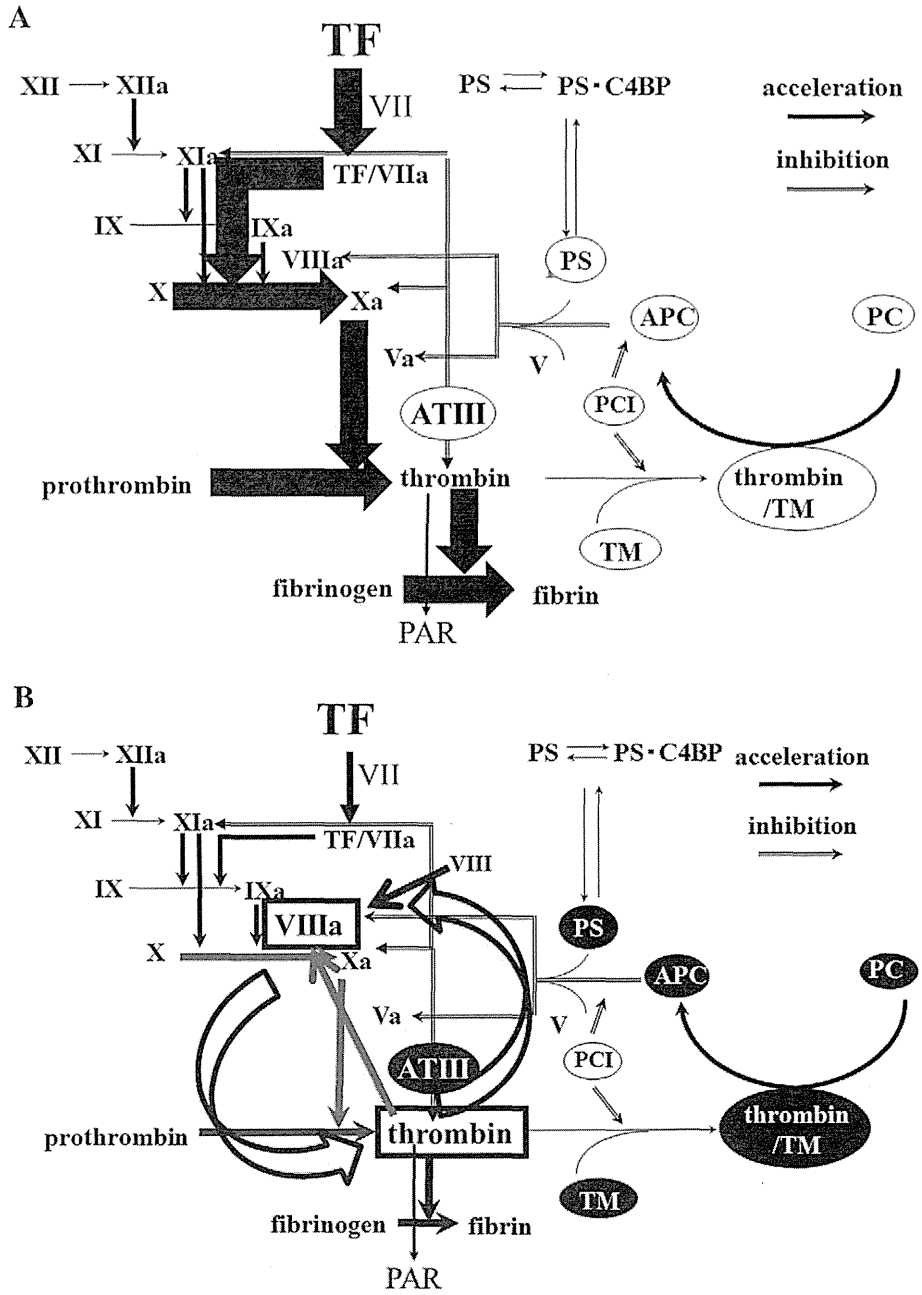

Fig. 2. A Mechanism of the activation for the coagulation system in DIC patients with leukemia. B Mechanism of the activation for the coagulation system in DIC patients with sepsis.

B (NF-κB), which results in the production of various inflammatory cytokines [20,21] as well as TF. Markedly high expressions of TF messenger RNA have been reported in leukocytes obtained from septic patients with DIC [36]. Both the AT and PC levels are significantly low in septic patients with DIC [19,40], and a reduced amount of AT and PC results in the lack of inhibition of thrombin and activated FVIII, respectively. Thrombin activates FVIII, while activated FVIII accelerates the coagulation pathway to generate thrombin; thus, activation of the coagulation system persists (**Fig. 2B**). In addition, elevated soluble platelet glycoprotein VI [41] and reduced ADAMTS13 [42] levels have been reported in patients with DIC, suggesting that platelets are also activated due to the reduction of ADAMTS13 in septic patients with DIC. (See Fig. 3.)

The fibrinogen and fibrin degradation products (FDP), plasmin–plasmin inhibitor complex (PPIC) and fibrinogen levels are significantly different between hyperfibrinolytic DIC and non-DIC patients, and the platelets, soluble fibrin (SF), thrombin AT complex (TAT) and AT levels are significantly different between septic DIC and non-DIC patients. Therefore, these markers are useful for differential diagnosis between hyperfibrinolytic type of DIC and organ failure type of DIC.

2.2. DIC diagnostic criteria

Three diagnostic criteria are primarily used by physicians in Europe, North America and East Asia. The diagnostic criteria of the ISTH for overt-DIC [8] were established based on a modification of the JMHW DIC diagnostic criteria in 2001 [7]. In a retrospective study using the JMHW diagnostic criteria [28], the treatment of early-stage of DIC was reported to be effective. In 2005, the Japanese Association for Acute Medicine (JAAM) published diagnostic criteria for DIC involving the use of global coagulation tests, systemic inflammatory response syndrome (SIRS) [43] scores and changes in global coagulation tests [44,45]. As a gold standard for DIC does not currently exist, the patient outcome is often used to evaluate diagnostic criteria for DIC. Although these three diagnostic criteria score hemostatic abnormalities using similar global coagulation tests, the cut-off values, as well as sensitivity or specificity for death, differ [46]. The sensitivity for 28th-day mortality is highest in the JAAM diagnostic criteria, although the specificity for 28th-day mortality is highest in the ISTH overt-DIC diagnostic criteria [46].

The ISTH criteria divide DIC into overt-DIC as non-compensated DIC and non- overt DIC as compensated DIC. The late onset of DIC from registration was previously reported to be classified as pre-DIC [1,2].

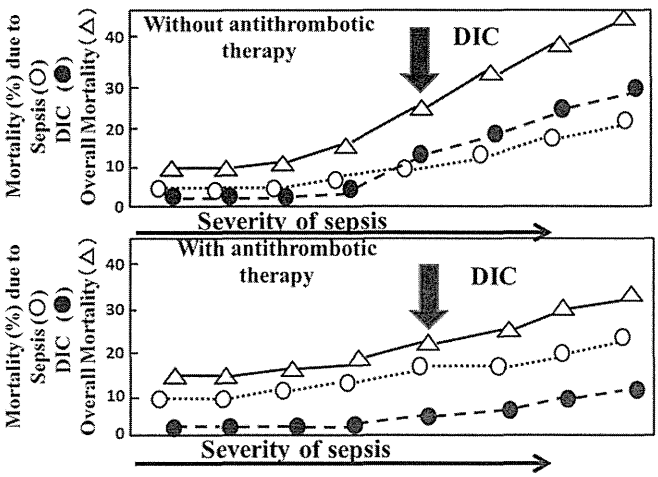

Fig. 3. Outcomes of septic DIC treated with and without antithrombotic therapy.

There are no significant differences in the frequency of late-onset DIC from registration between the three diagnostic criteria for DIC, suggesting that it is difficult to diagnose pre-DIC according to the DIC score using global coagulation tests [46]. Therefore, the ISTH also proposed non overt-DIC diagnostic criteria involving the use of global coagulation tests, changes in global coagulation tests and hemostatic molecular markers [8], although this template has not been established. Therefore, several modified versions of non-overt-DIC diagnostic criteria using global coagulation tests, changes in global coagulation tests, AT and hemostatic molecular markers have been proposed [47-51].

2.3. Outcome and diagnosis of DIC

The mortality of severe sepsis patients treated with AT [10], rh APC [11] and rhTFPI [13] and that of DIC patients treated with rhTM [15] and plasma-derived APC [14] has been reported to be 37.5%, 24.0%, 34.6%, 28.0% and 20.4 %, respectively. The mortality of septic patients varies depending on the severity of sepsis, including the association with DIC. Among placebo-treated patients with severe sepsis, the mortality of non-DIC patients is approximately 22%, while that of placebo-treated patients with DIC is 40–45% [52], suggesting that complication with DIC worsens the outcomes of patients with sepsis. Taking into account bias from physicians, the mortality of patients treated with rhAPC or rhTM is approximately 25–28%. In cases of infection, treating DIC may reduce mortality by 10–15%. However, in several randomized controlled trials [10,12,15], treatment with AT, rhAPC or rhTM did not significantly reduce mortality in patients with sepsis in comparison to a placebo. In a subclass analysis, AT was found to reduce mortality in patients with severe organ failure [53] and in those with DIC [54], but not in those with mild organ failure. APC has also been reported to reduce mortality in patients with severe, but not mild, organ failure [53].

The sensitivity for death among patient with DIC is highest in the JAAM diagnostic criteria, although the specificity is highest in the ISTH overt-DIC diagnostic criteria [46]. While it has been reported that early treatment reduces mortality when using the JMHLW DIC diagnostic criteria [28], the odds ratio for 28-day mortality is similar between the JMHLW, ISTH and JAAM diagnostic criteria [46]. A recent multicenter, prospective validation study of the JAAM criteria [55] showed that the 28th-day mortality was similar between DIC patients diagnosed according to the ISTH overt-DIC diagnostic criteria and those according to the JAAM criteria, suggesting that the JAAM and ISTH-overt DIC criteria exhibit similar sensitivity for 28th-day mortality [55].

As the presence of NETs [22] and hypercoagulation observed in patients with DIC induce localization of infection, the administration of antithrombotic therapies, such as AT and APC, may spread the infection. Treatment with AT or APC may worsen sepsis in the early stage of the disease, while improving hemostatic abnormalities following organ failure in patients with severe sepsis. In total, treatment with AT or APC may not improve the outcomes of patients with sepsis in the early stage, although it can potentially improve the outcomes of those with DIC. The timing of AT or APC treatment may be too early in septic patients when using only the JAAM diagnostic criteria and too late in those with overt-DIC.

Therefore, new diagnostic criteria for determining the appropriate time to initiate anticoagulant treatment are required.

Acknowledgments

This work was supported in part by a Grant-in-Aid from the Ministry of Health, Labour and Welfare of Japan for Blood Coagulation Abnormalities (H23-general-002) and the Ministry of Education, Culture, Sports, Science and Technology of Japan (H23-general-002).

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CRITICAL CARE

LETTER

Is early treatment of disseminated intravascular coagulation beneficial in septic patients?

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See related research by Gando et al., http://ccforum.com/content/17/3/R111

We read with interest the recent issue of *Critical Care*, particularly the article by Gando and colleagues [1] about the validation of the scoring systems for disseminated intravascular coagulation (DIC). Mortality in patients with DIC according to diagnostic criteria of the Japanese Association of Acute Medicine (JAAM; 31.8%) was similar to that in patients with International Society of Thrombosis and Haemostasis (ISTH) overt-DIC (30.1%). A previous report [2] showed different results; mortality was significantly higher in patients with overt-DIC (34.4%) than in those with JAAM DIC (17.2%). The difference in the mortality between this report [1] and the previous report [2] may depend on not only the sensitivity of the diagnostic criteria, but also on the antithrombotic therapy (ATT).

Although most patients were considered to be treated with ATT at the early stage of DIC in this study [1], those treated in the other study [2] had late stage DIC [3]. As the presence of neutrophil extracellular traps [4] and hypercoagulation in DIC induce localization of infection, the administration of ATT may spread the infection. Therefore, ATT may worsen sepsis in the early stage of the disease while improving hemostatic abnormalities following organ failure in patients with severe sepsis. Overall, ATT may not improve the outcomes of patients with sepsis in the early stage, although it can potentially improve the outcomes of those with overt-DIC (Figure 1). The timing of ATT may be too early in septic patients when using the JAAM diagnostic criteria and too late in those with ISTH overt-DIC.

Authors' response

Satoshi Gando

We appreciate the interest of Wada and colleagues in our recently published article studying the JAAM DIC scoring system in patients with severe sepsis [1]. It is now widely accepted that localized platelet and fibrin thrombosis at the site of infection is a physiologic reaction that protects against dissemination of microorganisms and pathogen-associated molecular patterns derived from them into the systemic circulation, which is now called immunothrombosis [5]. Therefore, we agree that early anticoagulation therapy for sepsis probably induces uncontrolled immunothrombosis, leading to pathological systemic DIC. Fourrier [6] clearly demonstrated that the target for the treatment of sepsis is not sepsis itself, but DIC as a result of the overwhelming effects of sepsis on immunothrombosis. The mortality rate of the severe sepsis patients who met the JAAM DIC criteria was 31.8%, and the Kaplan-Meier curves clearly demonstrated that there was a lower 1-year survival rate in the JAAM DIC patients, which supports our opinion that the DIC patients diagnosed by the JAAM scoring system should be treated as early as possible [1]. The differences in the mortality rate between the two studies pointed out by Wada and colleagues were due to differences in the subjects included in the two studies [1,2]. Our previous study included diverse clinical conditions that were associated with DIC [2], but the inclusion criteria for the current study were restricted to only severe sepsis patients [1].

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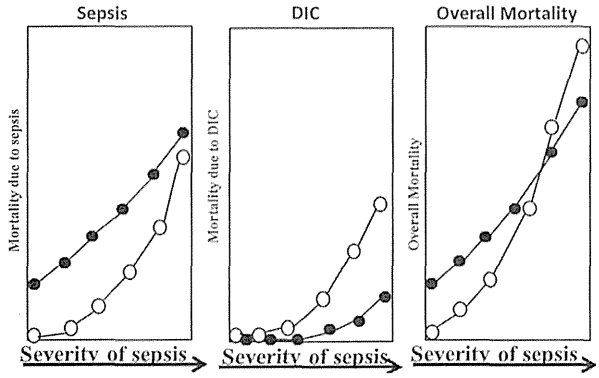

Figure 1 Mortality due to sepsis and/or disseminated intravascular coagulation (DIC). Open circles indicate without DIC treatment, closed circles with DIC treatment.

Abbreviations

ATT: antithrombotic therapy; DIC: disseminated intravascular coagulation; ISTH: International Society of Thrombosis and Haemostasis; JAAM: Japanese Association for Acute Medicine.

Competing interests

The authors declare that they have no competing interests.

Acknowledgments

This work was supported in part by a Grant-in-Aid from the Ministry of Health, Labour and Welfare of Japan for Blood Coagulation Abnormalities and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Published: 04 Jul 2014

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10.1186/cc13971
Cite this article as: Wada *et al.*: Is early treatment of disseminated intravascular coagulation beneficial in septic patients? *Critical Care* 2014, 18:447

Thrombosis Research 134 (2014) 924–925

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Letter to the Editors-in-Chief

Addition of recommendations for the use of recombinant human thrombomodulin to the "Expert consensus for the treatment of disseminated intravascular coagulation in Japan"

Dear Editors,

When we published the "Expert consensus for the treatment of disseminated intravascular coagulation in Japan" [1], recombinant human thrombomodulin (rhTM) had not been marketed; therefore, recommendations regarding the use of rhTM were not stated at that time. A phase III trial of rhTM [2] subsequently showed the usefulness of this agent in treating disseminated intravascular coagulation (DIC), and the results of the postmarketing surveillance of rhTM guided by the Japanese Society on Thrombosis and Hemostasis (JSTH) confirmed the results of that trial [3]. In addition, the results of a phase II international trial of rhTM in patients with sepsis were also recently published [4]. Therefore, the JSTH would like to add a recommendation for the use of rhTM in the "Expert consensus for the treatment of disseminated intravascular coagulation in Japan."

Recommendation for the Use of rhTM

General: B1, asymptomatic type: B2, bleeding type (mild: B1, severe: C), organ failure type: B1, complication type: B2

B1: Treatment has moderately high quality of evidence, or it has high quality of evidence but the clinical usefulness is not significant.

B2: Treatment does not have a high quality of evidence, but it has few deleterious effects and it is carried out clinically.

C: Treatment does not have a high quality of evidence or the clinical usefulness is not clear.

Mechanisms of rhTM

Thrombomodulin (TM) exists on vascular endothelial cells and combines with thrombin. The thrombin-TM complex does not cleave fibrinogen, although it changes protein C into activated protein C (APC) [5]. APC inhibits the activity of coagulation factor VIII (FVIII) and FV by cleaving activated FVIII and FV using the protein S as a coenzyme. In addition, the thrombin-TM complex activates thrombin-activatable fibrinolysis inhibitor (TAFI) to inhibit fibrinolysis [6]. Since TM inhibits the complement system, it is considered to have an anti-inflammatory effect. In patients with sepsis, the expression of TM on vascular endothelial cells is down-regulated to a markedly low level by LPS and inflammatory cytokines. rhTM is a medication developed as a soluble protein containing an extracellular domain required to perform the activity of TM [7,8] and is considered to have an anticoagulant effect via APC production as well as antifibrinolytic and anti- inflammatory effects.

Evidence

In a Japanese phase III double-blind randomized control trial (RCT) of rhTM vs unfractionated heparin (UFH) in subjects with DIC [2], including 227 DIC patients with 125 hematological malignancies and 102 infections, the rate of resolution of DIC was 66.1% vs 49.9%, for absolute risk reduction of 16.2% (95%CI: 3.3% to 29.1%). The rate of disappearance of bleeding conditions was 35.2% in the rhTM group and 20.9% in the UFH group, for a difference of 14.3% (1.2% to 27.4%). In addition, the 28-day mortality among the patients with infection was 28.0% in the rhTM group and 34.6% in the UFH group, for a difference of 6.6% (-24.6% to 11.3%). The frequency of adverse events of bleeding was up to 7 days after the start of infusion significantly higher in the UFH group (56.5%) than in the rhTM group (43.1%), with no significant differences in other adverse events between the groups. In the present retrospective subanalysis of 80 patients with DIC secondary to infection [9] among the full analysis sample [2], the rate of resolution of DIC was 63.2% in the UFH group and 73.2% in the rhTM group, for a difference of 10.0% (95%CI:-10.5% to 30.5%). Furthermore, the 28-day mortality was 21.4% in the rhTM group and 31.6% in the UFH group, for a difference of 10.2% (-9.1% to 29.4%).

In an international double-blind placebo-controlled RCT [4] of 750 septic patients with suspected DIC, the 28- day mortality was 17.8% in the rhTM group and 21.6% in the placebo group, thus indicating a trend toward a low value, although the difference was not significant ($p = 0.273$), in the rhTM group. Furthermore, the values of hemostatic markers, such as D-dimer prothrombin fragment F1+2 and thrombin antithrombin complex, were lower in the rhTM group than in the placebo group, while there were no significant differences in the levels of inflammatory marker or rates of organ failure, bleeding, thrombosis or new infection. In the post hoc analysis, the greatest benefit from rhTM was seen in the patients with at least one site of organ system dysfunction and an international normalized ratio greater than 1.4 at baseline. This trial subsequently shifted to a phase III trial.

In a domestic postmarketing surveillance of rhTM among 3,548 patients with DIC (2,516 cases of infection and 1,032 cases of hematological malignancy)[3], the DIC scores were significantly decreased after treatment with rhTM in both groups ($p < 0.001$). The frequency of adverse drug reactions of critical bleeding was 2.6% in the infection group and 2.4% in the hematological malignancy group, with survival rates at 28 days after the last rhTM administration of 64.1% in the infection group and 70.7% in the hematological malignancy group.

Disclosure of Conflicts of Interest

The authors declare no potential conflicts of interest.

Acknowledgements

This work was supported in part by a Grant-in-Aid from the Ministry of Health, Labour and Welfare of Japan for Blood Coagulation

http://dx.doi.org/10.1016/j.thromres.2014.07.033

Abnormalities and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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6 May 2014

Natural History of Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

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Semin Thromb Hemost

Abstract

The differential diagnosis of thrombotic microangiopathy (TMA) has become clearer following the establishment of the relationships between (1) diarrhea-associated hemolytic uremic syndrome (HUS) and Shiga toxin–producing *Escherichia coli*–HUS (STEC–HUS), (2) a markedly reduced ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) level and typical thrombotic thrombocytopenic purpura (TTP), and (3) abnormalities in the complement regulatory system and atypical HUS (aHUS). These TMAs include typical TTP, other forms of TMA, STEC–HUS, and aHUS. The pathological mechanisms of TMA still overlap among several forms of TMA. With respect to the management of TMA, the use of plasma exchange (PE) for typical TTP, additional steroid therapy for TMA and rituximab for typical TTP with a high titer of the inhibitor of ADAMTS-13, as well as eculizumab for aHUS, have also been established. Although several issues remain in the pathophysiology and management of TMA, new findings will hopefully resolve these problems in the near future.

Keywords
- TTP
- TMA
- aHUS
- STEC–HUS
- ADAMTS-13

In 1955, Gasser and coworkers were the first to describe hemolytic uremic syndrome (HUS). Subsequent historical reports described a case where three similar recurrent episodes of hemolytic anemia, thrombocytopenia, and uremia occurred during an 8-year period.[1,2] The first cases of Shiga toxin–producing *Escherichia coli*–HUS (STEC–HUS) were found in the early 1950s, and the first clinical report in five children was published in 1995.[3] Thrombotic microangiopathy (TMA), including HUS and thrombotic thrombocytopenic purpura (TTP),[4–7] presents with specific symptoms, such as those involving microangiopathic hemolytic anemia (MHA), thrombocytopenia due to platelet consumption, and organ dysfunction. TTP is thought to be usually caused by an inhibitor of ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13)[8–11] and/or genetic abnormalities in ADAMTS-13, including Upshaw–Schulman syndrome (USS)[12]; however, other TMA patients who exhibit fluctuating neurological symptoms, renal injury and a high fever, may also be diagnosed with TTP. HUS comprises STEC–HUS[13] and atypical HUS (aHUS) with genetic abnormalities in the complement regulatory system,[14] although other forms of TMA associated with renal failure may be classified as HUS. In addition, TMA is observed in patients with severe sepsis,[15] disseminated malignancies,[16] malignant hypertension,[17] and disseminated intravascular coagulation (DIC).[18] Although the symptoms of TTP, USS, STEC–HUS, and aHUS are similar, the pathogenic mechanisms and effective treatments for these disorders differ among the types of TMA, requiring a differential diagnosis. By definition, HUS due to STEC is diagnosed as STEC–HUS. TMA associated with an ADAMTS-13 level of $< 10\%$ is classified as typical TTP, whereas patients with TMA in whom a diagnosis of typical TTP, STEC–HUS, or aHUS is excluded are considered to have another TMA. Individuals with TMA who exhibit an ADAMTS-13 level of $> 10\%$ in addition to relapse or a family history of TMA are diagnosed with aHUS (►**Table 1** and ►**Fig. 1**).

Issue Theme A Short History of Thrombosis and Hemostasis: Part II (40th Year Celebratory Issue); Guest Editor: Emmanuel J. Favaloro, PhD, FFSc (RCPA).

DOI http://dx.doi.org/10.1055/s-0034-1395154.
ISSN 0094-6176.

Table 1 Definition of TMA

TMA	TMA that has specific symptoms such as MHA, thrombocytopenia due to platelet activation and some organ dysfunctions.
Typical TTP	TMA with < 10% of ADAMTS-13
STEC–HUS	TMA due to STEC
aHUS	TMA which excludes typical HUS nor STEC–HUS and has > 10% of ADAMTS-13
Other type of TMA	TMA which excludes typical HUS, STEC–HUS, or aHUS

Abbreviations: ADAMTS-13: a disintegrin-like and metalloprotease with thrombospondin type 1 motif; HUS, hemolytic uremic syndrome; MHA, microangiopathic hemolytic anemia; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Clinical Characteristics of Thrombotic Microangiopathy

The patients with STEC–HUS usually have diarrhea, including bloody stool, and most patients with USS or aHUS have a family history of TMA and relapse. Neurological symptoms are generally dominant in typical TTP, and renal symptoms are generally dominant in HUS. Most cases of diarrhea-associated HUS are caused by STEC. The annual incidence of STEC–HUS is about 2 cases in adults and 6.1 cases in children younger than 5 years per 10^6 individuals.[3] High rates of STEC–HUS have been reported in regions of South America, especially Argentina, where HUS is endemic with an incidence 5 to 10 times higher than in North America. The incidence of aHUS may be less than 0.2 cases per 10^6 individuals. The annual incidence of acquired TTP in the United States is estimated to be 4 cases in 10^6 individuals and appears to be increasing.[19,20] For example, the Oklahoma TTP-HUS Registry includes 11.3 cases of TMA in 10^6 individuals[5] and 1.7 of cases associated with an ADAMTS-13 activity of less than 5% per 10^6 individuals.[21] Nara Medical University Registry includes approximately 0.84 of cases of TMA without STEC–HUS per 10^6 individuals in Japan,[22] while a questionnaire distributed in 2004 to 2005 by the Japanese Ministry, Health, Labor and Welfare (JMHLW) found approximately 2.0 cases of TMA with STEC–HUS per 10^6 cases individuals[23] (►**Table 2**). The incidence of USS may be approximately 0.05 cases per 10^6 individuals. Females are at greater risk, with a female-to-male ratio of at least 3:2[19] and 225:152.[23] According to the Oklahoma TTP-HUS registry, the clinical category can be classified as idiopathic (36.6%), additional or alternative disorder (25.9%), drug associated (12.3%), STEC–HUS (7.1%), pregnant/postpartum related (6.8%), allogeneic stem cell transplant associated (6.0%), and others (5.2%).[5] In addition, a questionnaire distributed by the JMHLW showed the type of TMA to be STEC–HUS (41.6%), typical TTP (20.9%), other TMA (10.1%), and TMA without measurement of ADAMTS-13 (27.5%).[23] Neurological symptoms were observed in 73.9% of patients with typical TTP and 44.6% of those with acquired TMA: renal dysfunction was detected in 40.9% of patients with typical TTP and 53.9% of those with TMA; and a high fever was noted in 72.3% of patients with typical TTP and 53.9% of those with TMA.[23] Unfortunately, approximately one-third of acquired TTP cases become chronic, and the management of significant morbidities remains a clinical challenge.[24,25] The patients with USS often present with severe unconjugated hyperbilirubinemia and Coombs-negative hemolytic anemia in the perinatal period. Peripheral blood smears usually show thrombocytopenia, red cell fragmentation and the leukoerythroblastosis as signs of MHA in patients with acquired TTP. As mentioned earlier, in contrast to patients with acquired TTP, subjects with familial TTP often respond well to simple plasma infusion, although nearly all such cases relapse.

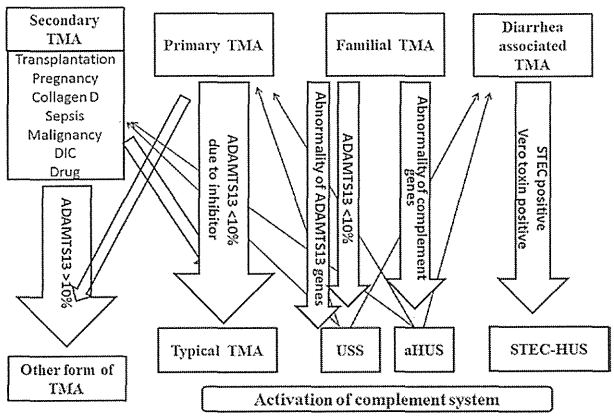

Fig. 1 Differential diagnosis of TMA. ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13); aHUS STEC–HUS, Shiga toxin-producing *Escherichia coli*–HUS; DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; atypical HUS, TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura; USS, Upshaw–Schulman syndrome.

Historical Overview and Pathogenesis of Thrombotic Microangiopathy

Many studies investigating the pathogenesis of TTP have historically focused on the roles played by endothelial cell injury and/or activation,[26] platelet abnormalities, and/or activation[26,27], abnormal von Willebrand factor (VWF) hemostasis,[28] abnormalities in the immune system,[29] prostacyclin binding defects,[30] and so on. Abnormal VWF hemostasis has recently become the most widely supported hypothesis regarding the pathogenesis of TTP. Upon vascular

Table 2 Frequency of TMA

Disease	Frequency	Area
TMA	4	United States[20]
TMA	11.4	United States (Oklahoma TTP-HUS registry)[5]
Typical TTP	1.7	
TMA	2.0	Japan (JMHLW)[23]
Typical TTP	0.4	
STEC–HUS	0.8	
TMA	0.8	Japan (Nara Medical University)[22]
STEC–HUS	18	World[3]

Abbreviations: HUS, hemolytic uremic syndrome; JMHLW, Japanese Ministry of Health Labor and Welfare; STEC, Shiga toxin-producing *Escherichia coli*; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.
Note: Frequency in 10^6 populations.

endothelial cell stimulation or injury, the stored VWF is released from Weibel–Palade bodies[31] into the circulation in a form that is termed unusual large VWF multimer (UL-VWFM), which represents the most thrombogenic form of this molecule.[32] UL-VWFMs are processed into smaller and less thrombogenic multimers by VWF cleaving protease (later identified as ADAMTS-13); therefore, UL-VWFMs are not detected in healthy human plasma.[33] In 1982, the presence of UL-VWFMs was demonstrated in the plasma of patients with USS,[34] suggesting a crucial link between the pathogenesis of TTP and metabolism of VWF. These findings indicate that

UL-VWFMs play an important role in the formation of platelets and VWF-rich clots characteristic of TTP and that a deficiency in VWF cleaving protease is the underlying cause of TTP. In 2001, this VWF cleaving protease was ultimately identified as the metalloproteinase ADAMTS-13.[8–10,35] This enzyme cleaves VWF within the A2 domain between amino acid residues tyrosine 1605 and methionine 1606.[36] The in vitro activity of ADAMTS-13 is dependent on the degree of conformational changes induced by shear stress[37] and mild denaturants, such as guanidine or urea,[38,39] suggesting that the cleavage of VWF by ADAMTS-13 in vivo is dependent on factors such as fluid shear stress and binding to platelets, the vascular endothelium, or possibly other molecules.[39] The deficiency of ADAMTS-13 may be caused by genetic mutations[40] or acquired factors, such as the actions of anti-ADAMTS-13 inhibitors[41,42] and/or consumption due to sepsis.[43]

Genetic Abnormality of ADAMTS-13 (Upshaw–Schulman Syndrome)

Although classic USS involves severe neonatal jaundice requiring plasma exchange (PE) or blood transfusions, and repeated childhood episodes of MHA can be reversed by the infusion of fresh frozen plasma (FFP),[12] recent reports have indicated that the clinical signs of USS during childhood may be milder than expected, with only isolated thrombocytopenia in many cases.[44] USS is rare, with an estimated 100 patients (approximately) worldwide following the discovery of ADAMTS-13.[45,46] Around 60% of these cases involve missense single amino acid substitutions, with the remaining 40% being nonsense, frameshift or splice site mutants expected to result in truncated proteins. In vitro studies of several missense mutants have demonstrated impaired secretion in cell culture media.[47] These studies found that impaired secretion into the circulation may be the dominant mechanism underlying ADAMTS-13 dysfunction and that most patients with USS have absent or nearly absent ADAMTS-13 antigen levels.[48] According to the Nara Medical University registry,[22] a total of 41 USS patients have been identified in 36 different families, ranging in age from early childhood to 79 years.[12] Furthermore, analysis of a large cohort of patients with familial TTP revealed the age-dependent clustering of cases into two relatively distinct groups, with approximately half of patients exhibiting disease onset within the first 5 years of life and the other portion remains asymptomatic until 20 to 40 years of age.[49] Examples of siblings with the same ADAMTS-13 mutations but markedly different clinical courses have also been reported.[49,50] Therefore, in patients with familial TTP, ADAMTS-13 deficiency in and of itself does not appear to be sufficient for disease onset.

Acquired Deficiency due to Inhibitor (Typical Thrombotic Thrombocytopenic Purpura)

Although the level of ADAMTS-13 activity defining severe deficiency has not been established, an ADAMTS-13 activity less than 5% is specific for syndromes associated with the typical clinical features of TTP.[5,21] This stringent definition of severe ADAMTS deficiency excludes some patients with typical features of TTP, including multiple episodes of relapse. However, some studies have expanded the definition of severe deficiency to include all patients with an ADAMTS-13 activity less than 10%.[51] The inhibitor of ADAMTS-13 can be measured using an ADAMTS-13 activity assay,[52] and an ADAMTS-13 activity less than 5% suggests a high probability for the presence of an inhibitor in TTP patients.[6] In addition, it has been reported that TTP patients with high titers of inhibitors for ADAMTS-13 have poor outcomes.[53] In patients with an ADAMTS-13 activity lower than 5% without inhibitors, PE may result in complete clinical remission and an increase in the ADAMTS-13 level. In contrast, other patients with a low ADAMTS-13 activity but high titer of inhibitor (> 5 units/mL) display neither a rise in the ADAMTS-13 activity nor a reduction in the inhibitor titer.[54] Autoantibodies to ADAMTS-13 often develop in patients treated with antiplatelet agents (drug-associated TTP).[55] Some patients experience persistent severe ADAMTS-13 deficiency, with a demonstrable titer of inhibitor but no signs of TTP after recovery, suggesting that ADAMTS-13 deficiency alone is not sufficient to cause TTP.

Consumption of ADAMTS-13

Although there are reports of a markedly decreased ADAMTS-13 activity without inhibitors in patients with severe sepsis,[43,56] severe liver disease,[57] liver transplantation,[58]

disseminated malignancies,[16] malignant hypertension,[17] and DIC,[59] these patients do not exhibit a typical clinical course of TTP, and the earlier-mentioned underlying diseases have subsequently been discovered to more likely be the etiology of the presenting features in these cases. In addition, PE therapy is often not effective in TTP patients.[60] Most cases involving an ADAMTS-13 activity of < 10% are classified as idiopathic, with some patients presenting postpartum disorders (pregnancy-induced hypertension, hemolysis, elevated liver enzymes, and low platelet syndrome; HELLP syndrome), bone marrow transplantation, collagen diseases such as systemic lupus erythematosus, or treatment with specific antiplatelet drugs.[55]

Shiga Toxin–Producing *Escherichia coli*–Hemolytic Uremic Syndrome

Most cases of diarrhea-associated HUS are caused by STEC, and O157:H7 has the strongest association with HUS worldwide.[61,62] A cytotoxin active in Vero cells, less active in HeLa cells and inactive in WI38 cells (Vero toxin) was detected in stool isolates of *E. coli* from sporadic cases of HUS.[63] HUS is characterized by the presence of nonimmune hemolytic anemia, thrombocytopenia, and renal impairment,[3] and is the main cause of acute renal failure worldwide. This disorder occurs most frequently in children younger than 5 years, and its incidence is increasing.[61] This typical form of diarrhea-associated HUS induces toxin-mediated vascular endothelial cell damage, thrombotic occlusion of the capillary lumen, glomerular endothelial cell swelling, apoptosis of glomerular and tubular cell, and extensive cortical necrosis in the kidneys.[64] The severity of acute illness, particularly central nervous system impairment and the need for dialysis, is strongly associated with a worse long-term prognosis.[65] An outbreak that comprised 3,842 cases (including 54 deaths) of human infections with enteroaggregative hemorrhagic *E. coli* (EAHEC) O104:H4 occurred in Germany in May 2011. There was a high proportion of adults (845) affected in this outbreak and an unusually high number of patients that developed HUS. EAHEC strains have evolved from enteroaggregative *E. coli* by the uptake of a Shiga toxin 2a (Stx2a)-encoding bacteriophage.[66] The activation of the complement system has been reported in patients with STEC–HUS. The activation of an alternative pathway because of the upregulation of P-selection by Stx might be one of causes of this activation of the complement system.[3]

Atypical Hemolytic Uremic Syndrome

Approximately 10% of cases of HUS are classified as aHUS, as they are not caused by either STEC or streptococci.[3,67] aHUS has a poor prognosis, with death rates as high as 25% (67) and progression to end-stage renal disease in half of all patients.[3,68,69] Research has linked aHUS to uncontrolled activation of the complement system[69] due to mutations in complement factor H (*CFH*),[70,71] five CFH-related proteins (*CFHR1* through *CFHR5*),[72] membrane cofactor protein,[70,73] complement factor I,[70,74] complement factor B,[75] complement 3 (C3),[76] and thrombomodulin.[77] The complement system consists of several plasma and membrane-bound proteins that protect against invading organisms.[78] Three activation pathways—classic, lectin, and alternative—produce protease complexes termed C3 and C5 convertases that cleave C3 and C5, respectively, eventually leading to the formation of the membrane-attack complex.[69] Factor H antibodies are rarely detected in aHUS patients without a family history. The mechanism leading to factor H antibody production and disease onset are not completely understood.[79] *ADAMTS-13* mutations have been found in patients initially diagnosed with aHUS and Evans syndrome, suggesting that the diagnosis of USS is missed in many cases and thus the true incidence of this disease may be underestimated.[80] As noted earlier, the complement system has been reported to be activated in the patients with STEC–HUS, aHUS or typical TTP.[81]

Other Forms of Thrombotic Microangiopathy

TTP-like conditions also occur in association with a variety of clinical conditions, including cancer, bone marrow transplantation, collagen vascular diseases, and treatment with specific antiplatelet drugs.[82] Interestingly, many of these conditions appear to occur in the absence of ADAMTS-13 deficiency, suggesting the presence of different pathogenic mechanisms. The occurrence of TMA in pregnancy deserves special mention, as pregnancy has long been recognized to involve a prothrombotic state constituting a particular risk factor for episodes of both familial and acquired TTP. ADAMTS-13 deficiency also does not appear to be sufficient for the onset of acquired TTP. There are many patients with typical TTP who achieve clinical remission with PE continue to exhibit a persistent severe deficiency in the ADAMTS-13 activity and/or a significant amount of ADAMTS-13 plasma inhibitor and the patients with familial ADAMTS-13 mutations who have not yet developed clinically apparent TTP, despite the presence of ongoing severe ADAMTS-13 deficiency. These observations indicate that, in addition to ADAMTS-13 deficiency, additional genetic and/or environmental factors are required for the onset of both familial and acquired TTP. Environmental triggers potentially include infection, pregnancy, surgery, bone marrow transplantation, and certain medications, while possible genetic factors include those associated with the regulation of the coagulation cascade, VWF, or the platelet function as well as components of the endothelial vessel surface. The activation of alternative complement pathway by UL-VWFM has been described.[83]

Management of Thrombotic Microangiopathy

Guidelines for the diagnosis and management of TTP and other forms of TMA were published by the British Committee for Standards in Haematology in 2012.[84] The concept of the management of TMA will soon become common. Patients with familial TTP can be successfully treated with plasma infusions to supplement ADAMTS-13, while the mainstay of treatment for acquired TTP is PE, which is additionally thought to remove inhibitory autoantibodies. Although this therapy carries a considerable risk of morbidity, including exposure to blood products from multiple donors, the use of

PE has reduced the mortality of acquired TTP from 90 to approximately 20%.[24] In one comparison of the efficacy of PE and plasma infusion,[24] the short-term and long-term survival rates were higher in the PE group (24/51 and 40/51 patients) than in the plasma infusion group (13/51 and 25/51 patients), while the mortality at 6 months was lower in the PE group (11/51 patients) than in the plasma infusion group (19/51 patients).[24] In another prospective study,[54] the mortality rate was 15% among 20 patients with idiopathic TMA, including 16 subjects with TTP with an ADAMTS-13 activity of less than 5%, and 59% among those with secondary TMA. In addition, the response to PE was poor in the TTP patients with a high titer of ADAMTS-13 inhibitor. In retrospective studies, PE and other supportive therapies for TMA were found to be effective in 72.3% in Chinese patients[85] and 70.6% in the JMHLW study,[23] with a mortality rate of 29.4% in the Chinese study[85] and 19.6% in the JMHLW study.[23]

Patients with suspected or known ADAMTS-13 deficiency are also treated with glucocorticoids. Glucocorticoid therapy with PE also improves the mortality of TMA.[60,86] Patients who exhibit disease exacerbation despite receiving glucocorticoids may be treated with more intensive immunosuppressive agents, such as rituximab.[85] In a systematic review[87] of 27 patients treated with rituximab, a benefit was described in 25 (93%) patients. Meanwhile, in a prospective study,[88] 21 of 22 patients treated with rituximab survived, with a recovery in the platelet count within 35 days in all 21 survivors. In addition, in 7 RCTs of 476 young children with STEC–HUS, none of the evaluated interventions (FFP transfusion, heparin administration with or without urokinase or dipyridamole, ST-binding protein therapy, and steroids) were superior to supportive therapy alone with respect to any of the outcomes.[89] The outcomes of STEC–HUS have improved, and the acute mortality rate in children is 1 to 4%, and approximately 70% of patients recover completely from the acute episode.[90] In an outbreak of O104:H4, 491 patients with STEC–HUS were treated with best supportive care or therapeutic PE with or without eculizumab. Although the short-term outcome was better than expected when compared with previous reports, there were no significant differences in the

Table 3 Efficacy of treatment

	Therapy	Patients	Efficacy (%)
Canadian Apheresis Study Group[24]	Plasma infusion	TMA	40/51 (78.4)
	Plasma exchange		25/51 (49.0)
	Plasma exchange	TMA	72.3
Japanese Ministry of Health, Labor and Welfare[23]	Plasma exchange	TTP	32/64 (50.0)
		TMA	95/182 (52.2)
French TMA Reference Center[87]	Plasma exchange, vincristine	TMA	41/53 (77.3)
	Rituximab	TTP	21/22 (95.5)
Legendre et al[93]	Eculizumab	aHUS	88

Abbreviations: TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.

Table 4 Mortality

	Therapy	Patients	Mortality (%)
Canadian Apheresis Study Group[24]	PI	TMA	11/51 (21.6)
	PE		19/51 (37.3)
	Overall		30/102 (29.4)
Oklahoma TTP-HUS registry[5]	PE, steroid	TTP	7/45 (15.6)
JMHLW[23]	PE, steroid, etc.	TTP	12/54(22.2)
		TMA	64/327(19.6)
Zheng et al[54]	PE, etc.	Idiopathic TMA	3/20 (15.0)
	PE, etc.	Secondary TMA	10/17 (59.0)
Chinese study[84]	PE	TMA	15/51(29.4)
Bell et al[85]	Steroid ± PE	TMA	98/108 (9.3)
French TMA Reference Center[87]	Rituximab	TTP	1/22 (4.5)
Spinale et al[89]	Supportive theraoy	STEC–HUS	1–4

Abbreviations: HUS, hemolytic uremic syndrome; PI, plasma infusion; PE, plasma exchange; TMA, thrombotic microangiopathy; TTP, thrombotic thrombocytopenic purpura.