Trauma-Induced Coagulopathy

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1 Overview

Severe trauma has become a serious issue in modern society. More than three million people die of trauma each year worldwide, as the main cause of death for people under 44 years old, where, what's more, uncontrollable bleeding is the direct or indirect cause of death in the first 48 h after trauma. Coagulation disorders occur in about 1/3 of severely injured patients when they arrive at the hospital. The injured mainly died of massive hemorrhage in the early stage, while sepsis and multiple organ failure in the late stage. Massive traumatic hemorrhage can lead to hypothermia, acidosis, and blood coagulation disorders, which will promote each other to exacerbate the condition. Therefore, for massive traumatic hemorrhage, simple treatment of blood loss is not enough, but comprehensive management on a series of pathophysiological changes in the body caused by massive traumatic hemorrhage and subsequent multiple organ dysfunction, so as to reduce the mortality of patients.

Although the concept and relevant studies of trauma-induced coagulopathy have been put forward for nearly a century, its pathogenesis still needs clarification, because of multiple factors involved, such as anemia, blood dilution, hypothermia, acidosis, hemorrhagic shock, and the severe trauma itself. About 70 years ago, difficult hemostasis was noted in patients during major surgery, cardiac arrest, severe hemorrhage, shock, burns, emergency obstetric diseases, lung surgery, massive blood or fluid infusion, and tumor metastasis, which was named variously, such as severe bleeding tendency, defibrillation syndrome, consumption coagulopathy, etc., but all can be explained as hyperfibrinolysis, according to the observation and research at that time. In 1946, MacFarlane and Biggs, who summarized the research in the field of hematology believed that although the normal function of the hemostatic system was not clear, it could be activated during shock and proposed that shock was a common feature of different forms of hemorrhage. The predictions made by MacFarlane and Biggs more than 70 years ago marked a turning point in our understanding of hemostasis that the complex and in-depth issues revealed by their insights still arouse various thinking. In the 1970s, US military surgeons discovered the phenomenon of diffuse exudative coagulopathy during the rescue of the injured in the Vietnam War; trauma surgeon Hirsch described the phenotype of exudative hemorrhage accompanied by a shock that he had observed on the battlefield in Vietnam as a fatal and unchangeable outcome; Stefanini called such a hemorrhagic disorder as diffuse intravascular coagulation with fibrinolysis. In the 1980s, it was believed that early hemorrhage and coagulation disorders were secondary to the consumption, loss, or dilution of coagulation factors and platelets, which was exacerbated by acidosis and hypothermia. In 1982, Moore's research team called this coagulation disorder a vicious hemorrhage circle, and other researchers called it together with low temperature and acidosis as the lethal triad. In 2003, Brohi et al. introduced the term acute traumatic coagulopathy (ATC); others tended to use acute coagulopathy of trauma (ACoT), acute coagulopathy of trauma/shock (ACoTS), trauma-induced coagulopathy (TIC), or early trauma-induced coagulopathy (ETIC). In order to avoid unnecessary confusion in the literature, it is necessary to make a consensus on the name and abbreviation. According to the existing research materials on the pathophysiological changes of post-traumatic coagulation disorders, TIC seems to be the appropriate choice, which was also accepted by the National Institutes of Health (NIH) in 2010.

Although there is still no exact and accepted definition of TIC at present, the more agreed view is that TIC consists of multiple coagulation disorder processes, a clinic syndrome mainly manifested as coagulation dysfunction, caused by tissue damage after severe trauma or major surgery.

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The survival of injured patients depends on the regulation of these two opposing conditions, namely early hemorrhage and late thrombosis. Massive blood transfusion is commonly used to prevent the death of severely injured patients with massive hemorrhage in the early phase of trauma, but it can also negatively affect the outcome of trauma patients. The latest research shows that changes in coagulation function in the injured patient occurred before the consumption, loss, and dilution of coagulation factors or other traditional hypothetical factors, but the mechanism was not very clear. Therefore, understanding the pathophysiological changes and pathogenesis of TIC is of great significance to the management and blood transfusion of severe post-traumatic hemorrhage, which is also crucial to confirm the diagnosis, modify therapeutic strategies, and improve patient outcomes.

2 Pathogenesis

TIC is a syndrome characterized by blood exudation on the mucosa and serosal surface of non-surgical areas. The initiation of post-traumatic hemostasis concludes physiological changes and pathological changes (Table 1). The latter include initial endogenous pathology (directly caused by the trauma itself and/or traumatic shock) and secondary external pathology.

Small blood vessels contract immediately after the trauma in the early phase when manual hemostasis methods are recommended, such as compressing the wound and ligating the blood vessels. If hemorrhage and blood exudation occur in the non-traumatic areas besides the wound, coagulation dysfunction begins. The coagulation disorder directly caused by the trauma itself and/or traumatic shock is so different from the above-mentioned causes, such as blood dilution, hypothermia, and acidosis, that, sometimes, minor trauma can also cause extensive blood oozing. Therefore, it is important to make clear the difference between traumas in physiology and pathology to understand the pathophysiology of trauma-induced coagulopathy and improve therapeutic strategies.

Table 1 Changes in post-traumatic hemostasis [1]

Physiological changes	Pathological changes
• Hemostasis and wound healing	• Early changes induced by endogenous factors – Disseminated intravascular coagulation (DIC) Activated coagulation Insufficient anticoagulation Hyperfibrinolysis (early phase) Consumptive coagulopathy – Acute coagulopathy of trauma/shock (ACoTS) Coagulation inhibition mediated by activated protein C Hyperfibrinolysis mediated by activated protein C • Exogenous secondary DIC and ACOTS – Anemic coagulopathy – Hypothermic coagulopathy – Acidosis coagulopathy – Dilutive coagulopathy – Other factors

2.1 Classic Trigger Factors

2.1.1 Hemodilution

It has been believed for years that trauma-related coagulopathy is mainly caused by acidosis, hemodilution, and hypothermia after resuscitation with crystalloids. As the guide of advanced trauma life support (ATLS), patients with hypotension at admission could be infused with 2 L of crystalloid solution. In the early stage of hemorrhage, the small amount of fibrinogen and platelets stored in the body can be quickly lost; crystalloid resuscitation can further dilute the coagulation factors, thereby reducing blood viscosity. Resuscitation of pre-hospital crystalloids in severe trauma patients can worsen coagulation dysfunction, acidosis, and hypothermia and inhibit thrombin production. In 2013, a study by Cohen's team showed that severe trauma with an INR value greater than 1.3 was an independent risk factor for coagulopathy. Maegele, who has analyzed 8724 patients in the German Trauma Registry in 2007, has found that coagulopathy occurred in over 40% of those with crystalloid infusion greater than 2000 mL, more than 50% of those with crystalloid infusion greater than 3000 mL, and over 70% of those with crystalloid infusion greater than 4000 mL. Therefore, the amount of crystal resuscitation fluid should be limited during trauma resuscitation to reduce the dilution effect.

2.1.2 Hypothermia

The core body temperature of the severely injured is often lower than 36 °C. Hypothermia could promote trauma-induced coagulopathy. Heat production could be damaged by the rapid loss of a large amount of blood and the accompanying hypoperfusion. Besides, the production of thrombin will be slowed down, and its function will be inhibited below 36 °C. Mitrophanov analyzed the effect of low temperature and blood dilution on coagulation with a computer model and found that the prothrombin time of blood at 36 °C was prolonged to three times that of the normal.

2.1.3 Acidemia and Hypoperfusion

The impact of acidemia must be considered when blood clots are formed in the body. Engström et al. conducted an in vitro experiment in which a lower pH of a normal human blood sample combined with hydrochloric acid could slow down

the speed of thrombus formation with maximum clot strength, and the clot formation time with the pH value of 6.8 was extended by 168% when compared with that when the pH value was 7.4. Acidemia is the result of both crystalloid resuscitation (hyperchloremia) and hypoperfusion (hyperlacticaemia), which are difficult to separate. In the state of shock, when the perfusion for normal cell metabolism is insufficient, in such hypoxic conditions, the lactic acid produced by the anaerobic metabolism of cells helps the recovery of metabolic acidosis when the liver functions as normal. The over-physiological chloride concentration in normal saline, which leads to hyper-chlorinated metabolic acidemia, could aggravate the existing acidemia due to hypoperfusion in the injured. Hypoperfusion is also an independent factor that affects coagulation function. Simmons et al. reported that 777 patients with war trauma in shock state (alkaline deficiency BD<−6 mEq/L or systolic blood pressure < 90 mmHg) showed an abnormal increase in INR upon admission.

With the in-depth understanding of and attention to TIC, recent studies have shown that the role of these classic triggers has been exaggerated. A study by Brohi in 2003 found that TIC appeared before resuscitation, that 1/3 of patients with multiple injuries was diagnosed with coagulation disorders by routine laboratory examinations upon admission, with a few pre-hospital fluid infusion, no hypothermia, and no consumption of coagulation factors. Subsequently, Moore and Floccard also found, respectively, that there were 29% of patients suffering from coagulation disorders at 15 min after trauma and 56% of the patients at 25 min. In 2014, MacLeod also found that about 11% of patients with early trauma-induced coagulopathy were mildly injured (ISS < 16, normal RTS score, no fluid resuscitation therapy, stable vital signs). These studies and findings question the conventional beliefs that blood dilution, hypothermia, and acidosis trigger blood coagulation disorders. Attention has been paid to the possible relationship between the endogenous induction mechanism of early post-traumatic coagulation disorders and the location and features of the trauma.

2.2 Early TIC Mechanism

Regarding the mechanism of TIC, conventional views have focused on the consumption and dilution of coagulation factors, hypothermia, and acidemia. So far, it is still considered to be a component of the pathophysiology of TIC, but it is not the primary cause of TIC. The possible mechanism of TIC has been gradually revealed, which is a hypothesis that involves multiple factors, more complex than conventional doctrines. The current hypotheses of the mechanism of TIC include (1) DIC-fibrinolysis, (2) activated protein C, (3) glycocalyx, and (4) fibrinogen-centric hypotheses. TIC is a dynamic process changing over time. These hypotheses intersect with each other so that no single hypothesis can fully explain the various manifestations of coagulation dysfunction.

2.2.1 DIC-Fibrinolysis Hypothesis

DIC-fibrinolysis hypothesis believes that bleeding tendency is secondary to hypoperfusion/shock and endothelial injury, accompanied by prolonged PT, increased thrombin production potential, low antithrombin level, consumption of coagulation factors, decreased fibrinogen, increased fibrinogen degradation products (FDP), and increased FDP/D-dimer ratio. An excessive increase in plasmin activity instead of thrombin activity is considered hyperfibrinolysis.

For the same injury, the pathology of DIC and systemic fibrinolysis sometimes coexist, so it is called DIC with fibrinolysis phenotype. In addition to the secondary fibrinolysis caused by DIC, tissue-type plasminogen activator (t-PA) is released from the Weibel–Palade body of endothelial cells due to insufficient tissue perfusion caused by trauma, leading to systemic fibrinolysis. The levels of plasminogen activator inhibitor-1 (PAI-1) are almost the same in patients with or without DIC, while the levels of t-PA and plasmin α2-plasmin inhibitor complex, as the markers of plasmin production, are significantly higher than those without DIC, because of the extreme imbalance between t-PA and PAI-1, that the time is short from t-PA releasing from endothelial cells to its concentration reaching the peak, while several hours are required for the induction and expression of PAI-1 mRNA so that hyperfibrinolysis occurs immediately after trauma and lasts several hours.

Although fibrinolysis plays an important role in TIC, Letson et al. recently found in a rat model of hemorrhagic shock that a small volume of intravenous therapy of 7.5% adenosine/sodium chloride, lidocaine, and magnesium ions can fully recover the damaged coagulation function in 5 min, reverse hemorrhage in 20 min, and reverse shock in 60 min, indicating that TIC can be reversed because the animal models with early TIC did not suffer from DIC-consumptive coagulopathy. In another prospective cohort study, Rizoli et al. found that clinical manifestations of DIC did not occur in the severely injured assessed as DIC by scores according to the pathological results within 24 h after trauma. Therefore, the author believes that DIC is rare in severe trauma, and the ISTH (International Society of Thrombosis and Hemostasis) score is not a reliable prognostic indicator of DIC. Therefore, the early TIC, which is not DIC, has a distinctive feature of diffuse intravascular fibrin deposition. Although the in vitro thrombin generation potential is enhanced and/or fibrin and fibrin degradation products are increased, which all suggest the possibility of DIC, there is no clinically significant thrombosis state in vivo.

2.2.2 Activated Protein C Hypothesis

The activated protein C hypothesis also believes that hemorrhage is secondary to hypoperfusion/shock, vascular endothelial injury, and prolonged clotting time. However, hemorrhage is mainly stopped by activated endothelial protein C receptor (EPCR), thrombomodulin (TM), and TM-thrombin complex through activating the protein C (APC) pathway. APC inhibits the production of thrombin through the proteolytic inactivation of FVa and FVIIIa (enhanced by the cofactor protein S) to inhibit coagulation and also leads to a higher concentration of t-PA by inactivating PAI-1 so as to reduce fibrinogen to enhance the production of FDP and D-dimer, which ultimately promotes hyperfibrinolysis. In the first stage, when platelets and fibrinogen are relatively sufficient, microvascular thrombosis or DIC will not occur; the later thrombotic DIC is a unique clinical manifestation, which is an exhaustion of APC, clotting factors, and microvascular clots.

In addition to antithrombotic and antiplasmin effects, APC also has many important cytoprotective effects, such as anti-inflammation, anti-apoptosis, and endothelial barrier stabilization. The clinical results of multiple research teams support the protein C hypothesis.

The activated protein C has many properties that can explain TIC, but the basic mechanism is still unclear because APC is only moderately increased in TIC patients, indicating that it seems unlikely to be the only determinant or activator. In addition, the central principle of this hypothesis is that APC induces systemic anticoagulation by inactivating FVa and FVIIIa. It is difficult to observe an increase in thrombin production in TIC patients upon admission. However, it is possible that APC is a key point in the evolution of TIC over time.

2.2.3 Glycocalyx Hypothesis

The glycocalyx degradation hypothesis puts particular emphasis on the hypoperfusion/shock of endothelial injury and the trend towards DIC-fibrinolysis and activated protein C hypotheses. This hypothesis proposes to protect the negatively charged glycocalyx mesh, 0.1 μmol/L to 1 μmol/L in thickness, on the lumen side of the endothelium from damage or shedding. It is estimated that the destruction of glycocalyx may be caused by increased proteoglycan 1, resulting in systemic spontaneous heparinization leading to an anticoagulation state, which can be reversed by heparinase in some injured patients. Glycocalyx degradation may further lead to the activation of endothelial cells and the subsequent imbalance between coagulation and inflammation, including local thrombin formation, fibrinolysis, leukocyte, and platelet dysfunction. Increasingly severe trauma and endothelial injury (increased proteoglycan 1) are manifested as prolonged APTT, enhanced sympathetic activity, exhausted protein C, increased soluble TM, hyperfibrinolysis, and inflammation.

In the early 1960s, Willoughby diagnosed a few post-catastrophic cases of postpartum hemorrhage with heparinized blood instead of de-fibrinolysis syndrome. This is still attractive even at present because this early hemorrhage may involve widespread endothelial damage, which supports the glycocalyx degradation hypothesis. The latest research indicates that endothelial damage may be reversible in a short period of time, which makes it a potentially valuable therapeutic target. However, except for the changes in proteoglycan 1, this hypothesis needs to be directly verified by intravital, electron, or confocal microscopy. The latest data from intravital microscopy support this hypothesis.

2.2.4 Fibrinogen-Centric Hypothesis

The fibrinogen-centric hypothesis is a relatively conventional hypothesis. Its roots can be traced back to the mid-1940s, but today it still attracts the attention of clinicians such as trauma, obstetrics, and cardiac surgery doctors. The focus of this hypothesis is that the loss of fibrinogen is the main driving factor of TIC, which reduces the amplitude of viscoelastic clots and increases FDP and D-dimer. Acute traumatic hypofibrinogenemia occurs when the breakdown of fibrinogen is faster than its synthesis, and the degree of fibrinogen loss depends on the severity of the trauma, shock, and the amount of infused fluid. Low fibrinogen may also change the platelet function and increase the activation of EPCR and TM-thrombin/protein C, which exacerbates the hemorrhage.

The fibrinogen-centric hypothesis is clinically relevant, especially in moderate to severe hemorrhage and shock. However, similar to the APC hypothesis, there are still various questions about how to link with the hemorrhage mechanism, such as the time of fibrinogen consumption, the role of FDP and soluble fibrin monomer, and the cause of possible defects in the cross-linking of fibrin through FXIII. The potential shortcoming of the current fibrinogen-centric hypothesis is that it ignores the number and function of platelets and erythrocytes when evaluating and treating coagulation disorders.

Although there are many hypotheses, animal models of different trauma types are still needed to further study their basic mechanisms, and prospective randomized controlled trials are urgently needed.

2.3 Others

Erythrocytes participate in hemostasis through four mechanisms, namely the rheological effect, adenosine diphosphate (ADP) release, production of eicosanoids regulated by platelets, and activation of the intrinsic coagulation pathway. Therefore, the reduction of hematocrit plays an important role in trauma-induced coagulopathy.

Red blood cells flow in the center of blood vessels, push platelets to move toward endothelial cells, increase shear force, and activate platelets. A low hematocrit value, regardless of the platelet count, can significantly reduce the platelet deposition in endothelial cells. When the platelet count is 50×10^9/L, and the hematocrit is 20%, there is almost no platelet deposited, but it can be compensated by increasing the hematocrit. Blajchman et al. have demonstrated that thrombocytopenia and low hematocrit levels can independently predict prolonged bleeding time and have believed that the formation of thrombi destroys erythrocytes and releases ADP. In addition, red blood cells participate in the production of thrombin through the exposure of procoagulant phospholipids. Red blood cells stimulate platelet to reactively induce eicosanoid production (thromboxane A2) to promote thrombosis. Factor XII or XI triggers the activation of the intrinsic coagulation pathway, leading to the stepwise activation of factors IX and X, inducing the production of thrombin. Intrinsic coagulation requires the activation of factor IX, which is activated by the erythrocyte elastase located on the erythrocyte membrane, and its activation can be exaggerated by increased hematocrit. The reaction of red blood cells on the platelet membrane plays an important role in the subsequent propagation of the coagulation waterfall. Experiments have shown that when a hematocrit reaches 33%, the bleeding time is improved, and thrombosis reappears, so it is generally believed that the hematocrit with the best hemostatic effect is 27–35%.

In short, although the basic mechanism of TIC cannot be explained well and uniquely, its main initiation is still related to tissue hypoperfusion, endothelial injury, and inflammation, various types and severity of trauma increase the complexity of its manifestations. The TM-thrombin complex and the fibrinolytic system of the endothelial cell are attractive therapeutic targets because they can act as a switch from fibrinolysis to anti-fibrinolysis. In-depth research will open up new diagnostic tools to reveal potential etiological factors and treat endothelial injury or other pathophysiological changes with new drugs. It is a challenge for early post-traumatic diagnosis and treatment to find the right balance point in the body.

3 Diagnosis

There are significant limitations in defining TIC according to laboratory standards. First, the pre-hospital emergency management of the injured is not entirely consistent. Many studies have excluded the patients who had received a large amount of crystalloid infusion before arriving at the hospital so that those with severe injuries may not be included leading to a data bias. Secondly, the laboratory equipment used to diagnose TIC does not meet the standards. Not every hospital has thromboelastography (TEG, Haemonetics, USA) or rotational thromboelastometry (ROTEM, Pentapharm, Germany). What's more, the laboratory testing of certain indicators takes longer. For example, in a study of 325 trauma patients, Davenport et al. found that the laboratory provided the electronic results of PT to clinicians for an average of 78 min. Finally, the patient's low hematocrit and the temperature of the POCT detection device may affect the accuracy of point-of-care testing (POCT). In other words, the difference between POCT and laboratory testing may lead to false-negative TIC. Nevertheless, there are still some laboratory indicators and clinical manifestations that help clinicians to judge.

3.1 Laboratory Diagnosis

3.1.1 Classical Coagulation Tests (CCT)

In 2010, Frith et al. retrospectively analyzed several major trauma centers in Europe and found that when shock and hemorrhage existed simultaneously, prothrombin time (PT) and activated partial thromboplastin time (aPTT) both increased significantly. In order to use these parameters to limit TIC functionally, they recommended the diagnostic criteria for TIC as the prothrombin time ratio (PTR, PTR = tested plasma PT value/normal reference plasma PT value) > 1.2. The patient's mortality and the need for blood transfusion were significantly increased above this threshold. The predictor, PTR, was helpful to discover 42.9% of patients with PTR > 1.2 that required a large amount of blood transfusion, with a negative predictive value of 98.4%. It was easier to find patients in need of massive blood transfusion by setting PTR >1.2 instead of 1.5 (17% more in probability).

However, the latest evidence shows that the classic coagulation test indicators, such as the international normalization (prothrombin time) ratio (INR), PT, aPTT, and fibrinogen (Fg), cannot accurately describe the complex process of acute trauma, because these classic tests are performed on platelet-poor plasma (PPP) samples so that the intensity of hemostatic clots cannot be assessed, leading to an increased false negatives incidence. These tests can provide fibrinogen content and platelet count, but their performance or function cannot be determined, as well as the condition of coagulation disorders, such as fibrinogen exhaustion, platelet dysfunction, or hyperfibrinolysis.

3.1.2 Viscoelastic Hemostatic Assays (VHA)

As the further understanding of the TIC triggering mechanism, laboratory tests of viscoelasticity have become more and more popular. Viscoelasticity tests, such as TEG or ROTEM, use whole blood and provide a result of the entire coagulation process, including information on the development, stability, and dissolution of blood clots, which reflects homeostasis.

Research by Jeger and Doran showed that there was a difference in sensitivity between the classic coagulation tests and TEG. Doran's data shows that 64% of the injured with coagulation disorders can be identified with abnormal description in the thromboelastogram in battle injuries, while the classic test (PT > 18 s) only has a 10% identification rate. Cotton et al. conducted a prospective study on 583 patients and compared the difference in time response between rapid TEG (rTEG) and classical coagulation test (CCT). Different from standard TEG, rTEG used tissue factor and kaolin added to the reagent to reduce the coagulation time by about 10 min. In Cotton's research, it was found that the results of R and K point in rTEG were displayed graphically within 5 min, and the results of MA value were visible within 15 min. There was a strong clinical correlation between activated clotting time (*R*-value in rTEG) and K-time with PT and aPTT, and a good correlation between α angle and MA with PT, aPTT, and platelet count. The activated clotting time measured by rTEG can determine whether there is a need for massive blood transfusion in the first 6 h after trauma.

By ROTEM, researchers have determined that the intensity of thrombi is weakening during TIC, which is weakened to 42% at 5 min, and such a situation continues until the blood clot is formed. Davenport studied 325 traumatic patients and found that the intensity of the clot was weakened, and the time for clot formation was shortened in ROTEM. With the threshold value of clot amplitude <35 mm within 5 min (CA5 < 35 mm), ROTEM can predict 77% of TIC, with a false-negative rate of 13%. Compared with the traditional coagulation test (PTR > 1.2), ROTEM can identify more TIC patients (18% vs. 8%). Davenport's research also shows that CA5 < 35 mm has a strong correlation with PRBC and FFP transfusion, where CA5 < 35 mm was used in 71% of the subjects to determine whether massive blood transfusion was needed, and PTR was used in 43%. Tauber has studied 334 injured patients with ISS > 15, with the results showing that ROTEM could accurately diagnose TIC and predict mortality and blood transfusion well, where the incidences of slowing down clot formation, reducing clot intensity, and impairing fibrin polymerization were 23%, 22%, and 30%, respectively. The viscoelasticity test appears to be superior to CCT in the management of TIC due to its diagnostic sensitivity and ability to guide clinical decision-making.

Although the viscoelasticity test analyzes the coagulation component dysfunction or defects through the indicators of whole blood coagulation, so that it has various advantages in guiding clinical treatment, it still has some limitations. Some parameters of standard TEG can be used in experimental research, such as functional fibrinogen (FF) to determine clot intensity, which is not routinely used in routine clinical practice. Similarly, rTEG is faster than standard TEG. In addition, the analysis software is often placed in the laboratory so that it is not convenient to provide real-time detection in the operating room, which limits its practicality in decision making in a rapidly changing environment. Finally, requires trained personnel are needed to operate the bedside TEG which is not daily examinations in the hospital, instead.

3.1.3 Platelet Function Analysis

Although conventional platelet count is a feature of post-traumatic platelet dysfunction, it has been replaced by another promising indicator, impedance aggregometry (IA), which has been validated by existing platelet function tests and bedside rapid analysis. The working principle of IA is to measure impedance through a stationary silver-coated copper wire in whole blood. If certain platelet agonists are added to whole blood, changes in impedance determine the functional activity of platelets. Commonly used agonists of platelet aggregation are collagen, adenosine diphosphate (ADP), arachidonic acid (AA), and thrombin receptor activating peptide (TRAP). The results can be obtained in about 10 min, and each test requires 300 μL of the blood sample. Research conducted by Kutcher indicates that although the platelet count was normal, the platelet function still has abnormal characteristics after trauma, and the platelet graph can reflect 45.5% of those with abnormal platelet function. Platelet graph or impedance aggregation will be a useful tool in the diagnosis of TIC in the future.

3.2 Clinical Diagnosis

The common properties of TIC-related studies have been quantified and graded through laboratory testing, and detailed laboratory data analysis of TIC is related to efficacy. The scope and investigation of coagulopathy phenotypes have been limited by the lack of a standardized clinical scoring system for coagulation disorders and criteria that can determine whether coagulation disorders affect mortality after injury. Although the clinical diagnostic criteria are still unclear, a resuscitation strategy for this clinical symptom has emerged. The definition of this clinical symptom currently relies on the subjective assessment of surgeons and the demand for blood products/transfusion. The establishment of a standard scoring system that can quantify, verify, and test the reliability of scorers for key clinical definitions is critical to clinical disease progression. NIH funded the establishment of the Trans-Agency Consortium for Trauma-Induced Coagulopathy (TACTIC), which contacted nationwide heart, lung, and blood institutes. The alliance

formed by TACTIC conducts research from large-scale multi-site clinical studies to basic mechanism laboratory investigations through the cooperative research between NIH and the Department of Defense on the issue of trauma-induced coagulopathy. In the design of a multi-center study, it is necessary to establish a scoring system that can quantify the severity of coagulopathy with criteria of significant clinical variables taken into account. The quantification of impaired coagulation and hemorrhage caused by coagulopathy rather than surgical bleeding (uncontrolled arterial or venous destruction) sometimes carries the risk of controversy and misclassification. In order to provide a balanced assessment and avoid assessing potential subjectivity, the scoring system adopts the five-point Likert scale (definitively positive, positive, possibly positive, suspected, and negative), and the observer must believe in the score of each stratification. Therefore, the following quantitative scoring system is proposed to evaluate TIC (Table 2).

One of the goals of the scoring system is to distinguish whether the injury that requires hemostasis is a mechanical trauma alone or hemorrhage with coagulopathy. Therefore, for a coagulation disorder with a score higher than I, the trauma surgeon must judge that the hemorrhage caused by severe trauma can not only be stopped by general hemostatic intervention. Besides, in order to further study coagulopathy, hemorrhage should be subdivided according to its source. The revised content includes the injury type with p for penetrating stab injury and b for blunt injury; the location of the injured should be considered when calculating the score, such as emergency department (ED), operating room (OR), or intensive care unit (ICU). Table 3 illustrates the examples of scoring different cases.

It is recommended that the attending trauma surgeon determine the evaluation score immediately or as soon as possible after the surgical hemostasis so as to obtain an initial impression of whether the patient has severe coagulopathy before resuscitation. Clinicians must make a clear distinction between bleeding from the injury site (uncontrollable surgical bleeding) and that due to coagulopathy in order to limit the assessment scores for trauma-induced coagulopathy. It is expected that the reliability of the score will increase as the injury time increases. The focus of the scoring system should be on controlling the bleeding amount after surgical hemostasis.

Table 2 Clinical scores of coagulopathy (I ~ V) [2]

Score	Description
I	Normal hemostasis. (No coagulopathy)
II III	Mild coagulopathy needs direct pressure or temporary gauze padding without other intervention required. (Coagulopathy is suspected.)
IV	Coagulopathy that is difficult to stop bleeding with direct pressure requires advanced hemostasis techniques (such as electrocautery, hemostatic agents, or sutures). (Coagulopathy is suspected.)
V	Although wound hemostasis has been performed, auxiliary blood products or systemic treatments are still needed for continuous bleeding. (Coagulopathy exists).
Sub-category	There are multiple diffuse and persistent hemorrhages far away from the trauma (such as tracheal intubation site, venous indwelling needle site, chest drainage tube, etc.) (Coagulopathy exists definitely.)
A	Isolated traumatic brain injury
B	Neck/chest/abdomen/pelvis injury
C	Extremity injury
D	Polytrauma[a]
E	Polytrauma + isolated traumatic brain injury

[a] The current consensus definition of polytrauma is a serious injury with AIS score > 3 points, two or more AIS anatomical parts, combined with one or more variables (systolic blood pressure ≤ 90 mmHg, Glasgow coma score ≤ 8 points, BE ≤ 6, age ≥ 70 years/o). The nature of the injury should be revised by an attending trauma surgeon, including blunt injury (b) or penetrating stab injury (p) after the mechanical bleeding is controlled

4 Treatment and Outcome

The two main causes of coagulopathy are surgical hemorrhage and non-surgical hemorrhage caused by trauma. Critical surgical hemorrhage is prone to induce hemorrhagic shock accompanied by extensive tissue damage. Their synergistic effects may cause DIC of the fibrinolytic phenotype. Therefore, the two main goals of TIC management are to control the hemorrhagic shock caused by severe trauma and severe hemorrhage, respectively. Early attention should be paid to the identification of high-risk factors, especially for the wounded with severe injury, severe traumatic brain injury, shock, active hemorrhage, and expected massive blood transfusion. The underlying disease should be treated actively, i.e., the trauma itself and shock caused by the trauma, because this is the main cause of systemic hyperfibrinolysis in the early stage of trauma. DIC could be controlled in the early stage of trauma, where it could be quickly reversed when hemorrhage and shock caused by trauma are controlled by surgery. Therefore, the multidisciplinary management of severe hemorrhage is the cornerstone of optimizing the treatment of injured patients.

The biggest controversy about TIC management is whether following the established protocol or the point-of-care (POC) goal-oriented treatment. The USA advocates established protocols to guide treatment, while Europe advocates POC goal-oriented to guide resuscitation. In addition, early and appropriate application of various hemostatic drugs is also advocated.

Table 3 Examples of clinical cases with TIC scoring system [2]

Clinical cases	Intervention/resuscitation	Location	Clinical scoring
1. Motorcyclists without helmets, severe traumatic brain injury; GCS: 3 points; CT: Intracranial hernia, active hemorrhage involves sites of scalp laceration, tracheal intubation, venous puncture site, and mucosa. 2. The patient was injured by a knife on a single limb with massive venous hemorrhage in the emergency department and was immediately sent to the operating room for surgery. After surgical hemostasis, there was continuous hemorrhage noted from an unknown part, which could be stopped after a few minutes of direct pressure on the suspected bleeding area. 3. The patient suffered from closed injury of multiple systems, grade III liver injury and moderate TBI (GCS 10 points), sent to ICU for non-surgical treatment. The third-level examination revealed a large area of scalp laceration with persistent non-pulsatile hemorrhage. The laceration continued to bleed after direct compression and suture. Due to a brief drop in the blood pressure, the patient was given several units of fresh frozen plasma and platelets because of the suspected continuous hemorrhage in the wound and abdominal injury. After the blood products were transfused, the bleeding on the scalp stopped, and the hemoglobin level remained stable after rechecking.	Manual compression to stop hemorrhage, application of blood products Only manual compression for hemostasis Blood products, wound suture	Emergency Department Operating room ICU	V-A(b)(ED) [Coagulopathy exists definitely.] II-C(p)(OR) [Coagulopathy is suspected.] IV-E(b)(ICU) [Coagulopathy exists.]

4.1 DIC with Fibrinolytic Phenotype

The key to DIC management is the preventive treatment of potential disorders, that is, the treatment of trauma itself and hemorrhagic shock. The main cause of hemorrhage induced by DIC with a fibrinolytic phenotypic is coagulation factor consumption and hyperfibrinolysis when anticoagulants are forbidden. The alternative therapy for coagulation factor consumption is to supplement concentrated platelets, fresh frozen plasma, and fibrinogen concentrate or cryoprecipitate, which can forcibly maintain the normal platelet count and coagulation level including antithrombin and protein C. At present, the infusion of FFP to maintain protein C and antithrombin may be a reasonable strategy for the treatment of post-traumatic DIC, which is important to inhibit the development of the fibrinolytic phenotype to the thrombotic phenotype. But the dosage of activated protein C, recombinant human thrombomodulin, and antithrombin needs to be noted, which, when exceeding normal levels, can cause hemorrhage.

Tranexamic acid, which can reduce the risk of hemorrhage and death in the injured, should be given as early as possible. Regarding the application of antifibrinolytic drugs in the injured, a global multi-center study is currently underway, of which the results may increase the theoretical evidence for antifibrinolytic therapy in patients with fibrinolytic DIC. However, within 24–48 h after the trauma, DIC with a fibrinolytic phenotype rapidly changes to DIC with a thrombotic phenotype, where patients should not be treated with antifibrinolytic drugs. In the randomized controlled trial (CRASH-2) conducted in 2011, 20,211 patients received tranexamic acid within the first 8 h after trauma. The results showed that the application of tranexamic acid within 3 h after trauma could reduce the mortality rate, while the application after 3 h may not be beneficial but cause harm.

Table 4 Bundling of trauma resuscitation [1]

Treatment of DIC with a fibrinolytic phenotype	Damage controlled resuscitation
• Following disorders – Surgical hemorrhage caused by or secondary to trauma – Hemorrhagic shock • Coagulation factor consumption • Hyperfibrinolysis	• Damage control surgery • Permissive hypotension – Restrictive infusion – Sufficient perfusion pressure • Hemostasis and resuscitation – Fixed blood transfusion ratio – Fibrinogen concentrate – Prothrombin complex – Reorganization FVIIa – Tranexamic acid

4.2 Severe Hemorrhage and Hemorrhagic Shock

In the past decade, based on the experience of military medicine and the progress of TIC research, the method of massive blood transfusion in severe hemorrhage has been greatly improved, which is now called damage control resuscitation. Damage-controlled resuscitation usually consists of damage-controlled surgery, permissive hypotension, and hemostatic resuscitation; however, during the damage-controlled resuscitation, which should be considered as a bundled type from the trauma site to the emergency room, operating room, and ICU, the traumatic resuscitation should cover the following therapeutic protocols during the treatment (Table 4).

4.2.1 Damage Control Surgery and Permissive Hypotension

Damage control surgery includes simple surgery, primary suture of the surgical site (primarily in the abdomen), correction of hypothermia and coagulopathy, and reoperation plan (allowing the injured to recover physiological reserve func-

tion before surgery). Although there are no randomized controlled trials to evaluate the procedure of damage control surgery, this concept has now become the guiding principle of trauma surgery.

Due to a non-randomized trial conducted in the mid-1990s, the concept of permissive hypotension (defined as restricting infusions until the hemorrhage is controlled) spread across the world. However, a Cochrane review showed no difference in mortality between early and delayed (restrictive) resuscitation. There is no evidence to support the mandatory use of permissive hypotension and sufficient cerebral perfusion pressure in patients with traumatic brain injury. The primary goal of the management of severe hemorrhage and hemorrhagic shock is to deliver oxygen to peripheral tissues and organs to counteract the oxygen debt and restore oxygen supply. Oxygen transport is to maintain adequate cardiac output through proper blood volume and perfusion pressure, and it is also coordinated by oxygen carried by hemoglobin and dissolved in plasma. The problem with permissible hypotension is that using this term makes the specific definition of restrictive infusion unclear. In order to maintain adequate perfusion pressure, this misleading term should be more accurate, so that it is currently recommended to describe it as the mean arterial pressure $\geq$ 80 mmHg.

4.2.2 Goal-Directed Hemostatic Resuscitation

The prevention and treatment of coagulopathy has gradually received attention since whole blood resuscitation in the 1970s to the extensive application of massive crystalloid solution and oxygen resuscitation, especially the current damage-controlled surgery (DCS) theory to trauma resuscitation, where the most representative new theory is early goal-directed coagulation therapy (EGCT). The embryonic form of this diagnostic, guided therapy is to guide component blood transfusion based on the results of viscoelastic hemostatic assays (VHA), then it developed into goal-oriented hemostatic resuscitation and finally formed EGCT. The short time required for VHA provides the possibility of rapid diagnosis and individualized treatment, and dynamic detection can be used to continuously evaluate the treatment effect and further optimize the treatment plan to minimize the side effects of treatment. POC treatment is promoted in the guidelines published by the European Task Force for Advanced Bleeding Care in Trauma in 2013, where it was realized that early intervention could improve the abnormal coagulation indicators, reduce the overall demand for red blood cells, FFP, and platelets, and reduce the incidence of post-traumatic multiple organ failure.

It has become a common method to guide massive blood transfusion by laboratory tests or viscoelastic equipment to avoid excessive or harmful use of blood products, which is called goal-directed hemostatic resuscitation. Many studies have suggested the application of viscoelastic devices in this strategy, which can provide a more comprehensive observation of the coagulation function of the injured. It has been proved that rapid TEG at admission has great advantages compared with conventional coagulation indicators (PLT, PT, PTINR, aPTT, and fibrinogen). However, a Cochran report confirmed that for patients with severe hemorrhage, neither ROTEG nor TEG could improve their mortality. The DIC scoring systems of the International Society on Thrombosis and Haemostasis (ISTH) and the Japanese Association for Acute Medicine (JMMA) include the parameters of inflammation, platelets, coagulation, and fibrinolysis, which is beneficial to those who need hemostatic resuscitation in addition to hemorrhagic shock resuscitation. The DIC scoring system of JAAM at admission can independently predict whether the patient needs a massive blood transfusion, the morbidity, and the outcome of severe trauma patients. Therefore, the DIC scoring systems of ISTH and JAAM is promising method to guide goal-directed hemostatic resuscitation.

4.2.3 Fixed Proportion of Blood Product Transfusion

Hemostasis resuscitation, as a part of the massive blood transfusion strategy, is a treatment of severe hemorrhage and trauma-induced coagulopathy through the management of blood products to improve shock and hemorrhage and ultimately to control the development of DIC with a fibrinolytic phenotype to a thrombotic phenotype (DIC with a thrombotic phenotype is the reason for organ dysfunction). In spite of quite a few studies conducted in the past decade, there are few reports based on studies of hemostatic resuscitation.

Previous reports believed that sufficient plasma was important but did not provide an appropriate ratio. A fixed ratio of plasma and red blood cells of 1:1 in the treatment of coagulopathy due to war injuries, which has caused considerable controversy when proposed for the first time, has been accepted by many studies.

Recently, four systematic reviews and two meta-analyses have summarized the impact of a fixed proportion of blood transfusion strategies in trauma on mortality. The conclusions of the systematic reviews are almost the same that a high ratio of platelets or FFP to red blood cells can be associated with low mortality. The USA has summarized its experience through the wars in Iraq (Operation Iraqi Freedom, OIF) and Afghanistan (Operation Enduring Freedom, OEF) and recommended adopting a fixed ratio of packed red blood cells (PRBCs), fresh frozen plasma (FFP), and platelets (PLT) of 1:1:1 in the damage-controlled resuscitation for soldiers with acute trauma, according to the surgical research clinical practice guidelines of the Army Research Institute.

Based on the results of the prospective, observational, multi-center, major trauma transfusion (PROMMTT) study and retrospective analysis, a pragmatic randomized optimal

platelet and plasma ratios (PROPPR) trial was designed to assess the effects of different ratios of plasma, platelets, and red blood cells of 1:1:1 and 1:1:2 in predicting trauma patients who require a massive blood transfusion. There was no significant difference in mortality between the two groups. However, in the 1:1:1 group, more patients received hemostasis within 24 h and experienced fewer deaths after blood loss. This modified whole blood transfusion did not reduce the volume of blood transfusion in severely traumatic patients who had been predicted to require a massive blood transfusion.

Blood products containing plasma and platelets should be used in the early stage instead of a large number of crystalloids and red blood cells to replace the lost blood, which can reduce the occurrence of dilutive coagulopathy to a minimum; meanwhile, hemostatic resuscitation should be individualized based on the actual needs of the injured, according to the results of TEG. These two measures can not only reduce tissue perfusion insufficiency caused by inadequate blood transfusion and excessive hemorrhage caused by trauma-induced coagulopathy, but avoid increasing the risk of acute respiratory distress syndrome, acute lung injury, sepsis, and multiple organ dysfunction due to excessive blood transfusion. For patients with polytrauma but below the diagnostic criteria for hemorrhagic shock or without an indication for massive blood transfusion, DCR is not appropriate because the massive transfusion of plasm and platelets will increase the risk of multiple organ dysfunction but will not enhance their survival rate.

The amount and timing of FFP transfusion have been a topic of much controversy in recent years, mainly focusing on the optimal infusion ratio of FFP and RBC. Although many studies support the active application of FFP in the early stage of trauma, the optimal ratio of FFP to RBC is still inconclusive. In particular, the trauma of different severity and causes can directly affect the optimal ratio of FFP to RBC. Although there are no randomized studies on the application of DCR, many medical centers have adopted this view. But it is very difficult to accurately achieve this ratio, and the optimal ratio is still unknown. Some studies believe that compared with whole blood, this proportional blood component treatment (PRBCs:FFP:PLT = 1:1:1), which is similar to whole blood, provides lower hematocrit, fewer platelets, and lower coagulation factor activity. Therefore, many people believe that the most suitable resuscitation fluid is whole blood in patients with severe trauma who require a massive blood transfusion, which could also alleviate hemorrhagic shock and coagulopathy. At present, the only guideline that supports the application of whole blood before hospitalization is the Tactical Combat Casualty Care guidelines developed for tactical evacuation care.

4.2.4 Fibrinogen Concentrate

Fibrinogen can decrease to a very dangerously low level in the early phase of trauma. European treatment guidelines recommend that the fibrinogen of the injured should not be less than 1.5–2.0 g/L, below which fibrinogen concentrate (3–4 g) or cryoprecipitate (50 mg/kg or 15–20 U) should be used. In severely injured patients with hypofibrinogenemia, FC transfusion can reduce the application of other blood products and decrease the occurrence of hemorrhagic shock and MOF.

Fibrinogen, as the direct precursor of fibrin, is transformed by activating aggregation mediators of thrombin and platelet, playing the basic role of hemostasis. European guidelines define the critical value of fibrinogen as below 1.5 g/L before the critical value of platelet count, PT and aPTT appear within the first 24 h after the patient arrives in the emergency room. The fibrinogen level of patients with DIC decreased significantly when they arrived in the emergency room. Compared with patients without DIC, the former dropped to the critical value more quickly. The level of fibrinogen when arriving in the emergency department is an independent predictor of massive blood transfusion and death after trauma, and its optimal predictive value is 1.9 g/L or <1.5–2.0 g/L. These results clearly indicate that not all injured patients need to be treated with fibrinogen concentrate, and only those with DIC with a fibrinolytic phenotype should use fibrinogen concentrate.

After eliminating the cause of DIC, a fibrinogen concentrate is an important option for the treatment of hemorrhage induced by coagulopathy, including in trauma. However, there are still various contradictions and controversies in the use of fibrinogen in severe hemorrhage. Although there is a lack of evidence for the use of fibrinogen concentrate in injured patients with massive hemorrhage, and there are many methodological flaws in the included studies, some studies still show that fibrinogen concentrate management can reduce the demand for blood products. In the perioperative period, the effectiveness and safety of fibrinogen concentrate still need randomized clinical trials to solve this problem.

Fibrinogen concentrate does have the advantage of reducing the application of allogeneic blood products. Fibrinogen replacement therapy is being explored as a therapeutic strategy, such as fresh frozen plasma, other plasma products, or coagulation factor concentrates (such as prothrombin complex concentrate and recombinant FVIIa).

4.2.5 Prothrombin Complex Concentrate (PCC) and Recombinant Human Activated Factor VII (rFVIIa)

Prothrombin complex concentrate (PCC) is a concentrated product containing three (factors II, IX, and X) or four (factors II, VII, IX, and X) vitamin K-dependent coagulation fac-

tors. PCC contains no or very small amounts of anticoagulant proteins such as protein C, protein S (free), and fibrinogen-free antithrombin. In addition to the use of PCC to treat or prevent vitamin K antagonist-induced hemorrhage, PCC has been used in traumatic hemorrhage.

Many studies have confirmed increased thrombin production and lower levels of protein C, protein S, and antithrombin noted in DIC from immediately to a few days after the trauma. The production of thrombin in the circulation of such patients mainly depends on the reduction of antithrombin. Therefore, in theory, PCC, which has a very high ratio of procoagulant/anticoagulant, can induce thrombosis and DIC. In fact, PCC increases thrombin production with a decrease in platelet count and antithrombin levels, as well as prolongation of PT and APTT, which are similar to the progression of DIC. So it is recommended that PCC should be used cautiously based on the DIC score and the monitored antithrombin level.

The results of two randomized controlled trials on rFVIIa have been published. In the first study, it could only reduce the need for blood transfusion in patients with blunt trauma, but this study contained many methodological flaws; the second was terminated due to lower mortality than expected and ineffectiveness. A recent Cochrane systematic review concluded that the effectiveness of rFVIIa as a hemostatic drug had not been proven, while it can increase the risk of arterial diseases. Clinical trials should be restricted to using rFVIIa beyond the permitted scope.

Recombinant factor VII (rFVIIa) is a promising drug. A prospective study by Boffard et al. found that rFVIIa can reduce the amount of red blood cell transfusion in patients with blunt wounds, but there is no statistical significance in its effect on those with penetrating injuries and mortality. The available evidence suggests that there is no significant difference between patients treated with rFVIIa or placebo, and the former can also increase the probability of worsening DIC. Therefore, it is necessary to further study the efficacy and safety of rFVIIa in patients with fibrinolytic DIC.

4.3 Other Drugs

Considering that inflammation can trigger TIC, it is currently being studied to give patients non-steroidal anti-inflammatory drugs (NSAIDs) in the early post-traumatic phase. Prehospital use of NSAIDs can reduce the incidence of TIC. The conclusions drawn from these data are retrospective and observational, so further randomized controlled trials are needed to verify the significance of NSAIDs and whether they can develop another treatment for TIC.

Desmopressin is a synthetic arginine vasopressin analog that can promote the release of vWF from endothelial cells, increase the number of glycoprotein receptors on the platelet surface and the concentration of factor VIII in the blood, but there is no report on its application in trauma patients.

In terms of treatment, in addition to the above methods, we should also be alert to the hypercoagulable state and thrombosis secondary to TIC. An early study found that coagulopathy at admission is an independent predictor of venous thrombosis in trauma patients. Therefore, it is necessary to pay close attention to the risk of venous thrombosis and pulmonary embolism in such patients in the later phase.

5 Conclusion

Trauma-induced coagulopathy is an endogenous host reaction that occurs immediately after severe trauma. The activation of protein C, endogenous heparinization, and glycocalyx degradation are important initiating factors for TIC, and fibrinogen consumption and platelet dysfunction in hemorrhage must also be considered. The severity of trauma is related to the degree of coagulation. Classic coagulation tests cannot fully describe the complex process of TIC, so its value is limited. At present, it is mostly supported to adopt bedside coagulation function tests through TEG or ROTEM for early diagnosis. Early management includes rapid transportation from the scene to the hospital, surgical operation to control hemorrhage, avoiding excessive crystal fluid for resuscitation, and early identification of TIC. Protocol-guided treatment and PRBC:FFP: PLT = 1:1:1 is a promising strategy that has been widely used worldwide and has been proven to reduce mortality. Existing drugs, such as TXA which is now a standard treatment, should be used early. With our increased understanding of TIC, it is expected to establish standards for early diagnosis and treatment of trauma.

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