RESEARCH PORTAL CENTRAL

Proceedings of the International Academy of Sciences

OPEN ACCESS

Review Article

Diagnosis and Treatment of Disseminated Intravascular Coagulation: Shortcomings and Errors in Modern Guidelines

A.N. Belousov[1]*

1. Laboratory of Applied Nanotechnology of Belousov, Kharkiv National Medical University, Ukraine.

How to cite this article: A.N. Belousov (2025). Laboratory of Applied Nanotechnology of Belousov, Kharkiv National Medical University, Ukraine. Proceedings of the International Academy of Sciences. RPC Publishers. 2(1); DOI: https://www.doi.org/rpc/2025/rpc.pias/00142

***Address for correspondence:** A.N. Belousov, Laboratory of Applied Nanotechnology of Belousov, Kharkiv National Medical University, Ukraine. **Email:** an.belousov2012@ukr.net

Submitted: December 31, 2024
Approved: January 18, 2025
Published: January 25, 2025

Abstract

Disseminated Intravascular Coagulation (DIC) is a set of clinical manifestations of systemic thrombohemorrhagia. Despite the existence of numerous guidelines for the diagnosis and treatment of DIC, mortality from this condition remains high, ranging from 45% to 78%. The purpose of this study is to analyze the key provisions of leading guidelines and articles dedicated to the prevention, diagnosis, and treatment of DIC. During the study, conceptual errors were identified in the presented guidelines and articles, leading to false principles in the diagnosis, prevention, and treatment of DIC. A deep, comprehensive understanding of the functioning of the coagulation system, based on fundamental knowledge, is key to the correct assessment of its state and the choice of the most effective therapy method. The principles of diagnosis, prevention, and treatment of DIC should be based on the pathophysiology of coagulopathy development, clinical data, laboratory and instrumental studies, as well as an understanding of the mechanisms of action of therapeutic agents, taking into account an individual approach. Only the section on clinical transfusiology can provide the necessary professional knowledge on this topic, and a clinical transfusiologist is capable of diagnosing, preventing, and, if necessary, effectively correcting hemostasis in DIC.

Keywords: disseminated intravascular coagulation; conceptual errors in guidelines; diagnostic features; main principles of prevention and treatment; clinical transfusiology

Introduction

Disseminated Intravascular Coagulation (DIC) is a syndrome characterized by systemic activation of the blood coagulation system, leading to the formation of intravascular thrombin and fibrin, disruption of microcirculation in all organs and tissues, and subsequent development of increased bleeding [39, 44]. For better understanding, the most concise and comprehensive definition of DIC is the following: DIC is a set of clinical manifestations of systemic thrombohemorrhagia. This formulation contains key information. The first important phrase is "a set of clinical manifestations." This means that for the timely and rapid diagnosis of DIC, determining specific laboratory markers is not necessary; only the presence of a characteristic set of clinical symptoms is sufficient, which will be described in detail later. The second key phrase is "systemic thrombohemorrhagia." This indicates that the processes of thrombosis and hemorrhage are not only systemic in nature but also follow a strict sequence. Initially, the coagulation system is activated, leading to the formation of multiple microthrombi in the capillaries (hypercoagulation phase). Then, due to the activation of the fibrinolytic system, the microthrombi are destroyed, resulting in the formation of a large amount of their degradation products. This creates the conditions for the gradual transition from the hypercoagulation phase to the hypocoagulation phase. The latter is clinically characterized by the appearance of increased bleeding (hemorrhage).

DIC syndrome can develop as a complication of infections, solid tumors, hematological malignancies, obstetric pathologies, trauma, aneurysms, liver diseases, and other conditions, each of which has its own characteristics related to the underlying disease. Therefore, the diagnosis and treatment of DIC should take these features into account.

To date, there are three main guidelines for the diagnosis and treatment of DIC [8, 23, 45]. The first guideline was issued by the British Committee for Standards in Haematology (BCSH). The second was published by the Japanese Society on Thrombosis and Hemostasis (JSTH). The third was developed by the Italian Society on Thrombosis and Hemostasis (SISET). Despite their similarities, there are differences in the recommendations for the treatment of DIC. The DIC Subcommittee of the Scientific and Standardization Committee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH) consolidated these guidelines in a report titled "Guidance on the Diagnosis and Treatment of DIC,"

harmonizing the recommendations of all three guidelines [46]. The analysis of these guidelines raised many questions regarding the diagnosis, prevention, and treatment of DIC.

The main objective of this study is to analyze the key provisions of the leading guidelines and publications dedicated to the diagnosis, prevention, and treatment of DIC.

Pathophysiological Aspects of DIC

The authors of the presented guidelines, as well as some scientific articles, assert that hemostatic disorders in patients with DIC syndrome result from the sum of the actions of hypercoagulation and hyperfibrinolysis vectors. When the hyperfibrinolysis vector is pronounced and dominant, bleeding is the main symptom, and this type is referred to as hyperfibrinolysis-dominant DIC [8, 23, 17, 44, 45, 47].

This assertion is not only incorrect and misleading for clinicians, but it also contributes to a series of errors in the diagnosis and treatment of DIC. It is unclear what the authors mean by the sum of vectors. It should be reminded that hemostasis is ensured not by individual vectors but by the complex and coordinated work of numerous systems that maintain balance among the regulatory mechanisms of hemostasis. Speaking of blood systems, the main ones among them are the coagulation, anticoagulation, and fibrinolytic systems. It is important to note that the functioning of the first two systems directly depends on platelets. The number and functional activity of platelets determine the efficiency of the coagulation and anticoagulation systems of the blood. Additionally, it should be understood that the same mechanisms that initiate the coagulation process also activate factors of the blood's anticoagulation system. To better understand this, let's consider the interaction between the blood's coagulation and anticoagulation systems using a simplified example. On one hand, the formation of thrombin initiates the process of fibrin monomer complex polymerization and the conversion of fibrinogen into the soluble form of fibrin. On the other hand, the former thrombin, via thrombomodulin, activates the anticoagulant protein C, which hydrolyzes plasma factors V and VIII, ultimately limiting and regulating the blood coagulation process. As this example illustrates, when the coagulation and anticoagulation systems of the blood are balanced, the body does not need to activate the fibrinolytic system. The fibrinolytic system functions in a "normal" mode, which is confirmed by laboratory data showing reference values for D-dimer levels. The exception is isolated pathology within the fibrinolytic system. The assertion that bleeding is the main symptom when the hyperfibrinolysis vector is pronounced and dominant seems correct at first glance. However, in essence, this statement is incorrect and misleading for clinicians, which subsequently leads to improper treatment strategies for DIC. For example, in many protocols and publications, the use of lysine-containing fibrinolysis inhibitors is recommended. However, hyperfibrinolysis itself is not the cause of bleeding. Moreover, there are primary and secondary hyperfibrinolysis. Primary hyperfibrinolysis is caused by hyperplasminemia when a large amount of plasminogen activators enters the blood. In this case, increased bleeding may not be observed at all (Figure 1). Secondary hyperfibrinolysis develops in response to intravascular blood coagulation triggered by the entry of thromboplastic substances into the bloodstream (Figure 2). Plasminogen activators convert plasminogen into plasmin, which then causes the proteolysis of fibrin. As a result of proteolysis, fibrin degradation products (FDP) appear in the bloodstream. One of the reliable indicators of FDP is the D-dimer.

Figures 1 and 2 clearly demonstrate that even with the presence of hyperfibrinolysis and elevated levels of D-dimers, the hemostatic system can remain balanced. Therefore, the authors' assertion that bleeding is the primary symptom of hyperfibrinolysis is not correctly stated.

Secondary hyperfibrinolysis is a protective response of the body to thrombus formation activation. The primary goal of hyperfibrinolysis is to preserve the patient's life by timely dissolution of hemorrhagic clots and ensuring vessel patency (recanalization).

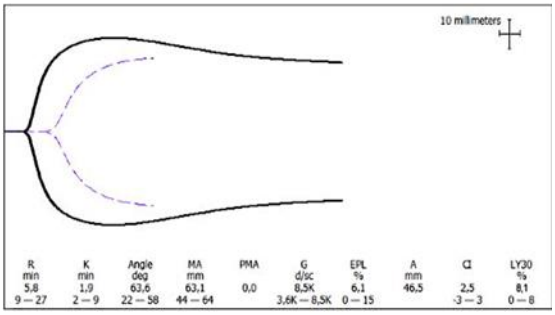

Figure 1: Clinical example of primary hyperfibrinolysis on TEG. Note: D-Dimer – 950 µg/l.

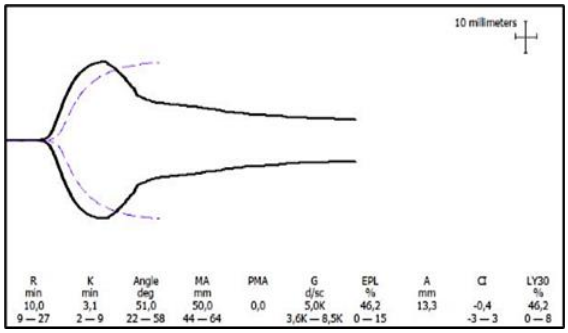

Figure 2: Clinical example of secondary hyperfibrinolysis on TEG. Note: D-Dimer – 700 µg/l.

However, it is important to understand the downside of hyperfibrinolysis as well. Hyperfibrinolysis results in the formation of a large number of fibrin degradation products (FDPs). It is the increase in FDPs that is the primary cause of heightened bleeding tendency and the development of the hypocoagulable phase of disseminated intravascular coagulation (DIC). FDPs inhibit the polymerization of fibrin-monomer complexes and also suppress platelet function. The mismatch between the increased levels of FDPs and the body's ability to eliminate them is the main and primary cause of the hypocoagulable phase of DIC (Figure 3).

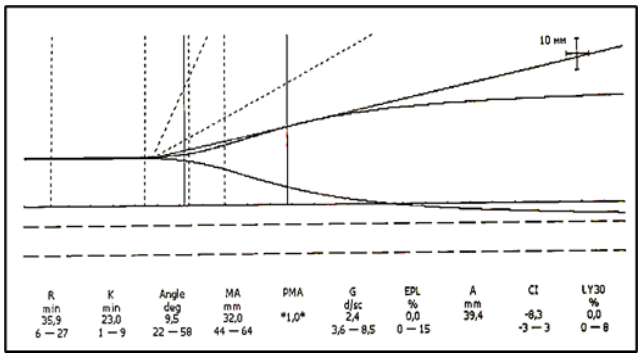

Figure 3: Clinical example of the development of the hypocoagulable phase of DIC on TEG (Platelets – 218 × 109/L; Hb – 129 g/L; Fibrinogen – 4.54 g/L; D-Dimer – 2500 µg/L).

FDP elimination occurs through phagocytosis. Therefore, the level of FDPs in the blood is directly dependent on the activity of phagocytes and the function of the reticuloendothelial system. The prolonged circulation of large amounts of D-dimers in the blood is one of the main reasons for recurrent bleeding in DIC. Thus, immunodeficiency, which inevitably arises from multi-organ failure syndrome, polypharmacy, or various iatrogenic factors, is a major reason for the reduced effectiveness of DIC treatment.

It is important to recognize that the use of serine protease inhibitors and lysine-containing amino acids only prolongs the thrombolysis process and thereby prevents a sharp increase in FDP concentrations in the blood. However, pathophysiologically, this does not fundamentally resolve the problem, due to various objective reasons.

Thus, the dominance of the hyperfibrinolysis vector is not a determining factor in the development of bleeding disorders, as suggested by the authors of the guidelines. Please note the difference in statements. Ultimately, clinicians' understanding of this issue determines their ability to provide an adequate, personalized approach to the comprehensive diagnosis and treatment of DIC.

Another incorrect assertion in the guidelines and articles is that elevated levels of cytokines [48, 49] and lipopolysaccharides (LPS) [44, 47] in the blood inhibit plasminogen activator inhibitor I (PAI-I), which ultimately suppresses fibrinolysis in DIC. It should be noted that the cytokine storm causes endothelial dysfunction rather than inhibiting plasminogen activators, as claimed by the authors. Indeed, endothelial cell damage can lead to reduced levels of tissue plasminogen activators (TPA). However, the authors overlook the fact that the fibrinolytic system is supported by more than just TPA. In addition to TPA, there are a range of internal fibrinolytic factors, the urokinase system, and bacterial fibrinolysis activators. On the contrary, during the hypercoagulable phase of DIC, there is a compensatory gradual increase in fibrinolysis, rather than a decrease. This is supported by the laboratory increase in D-dimer levels (Figure 4).

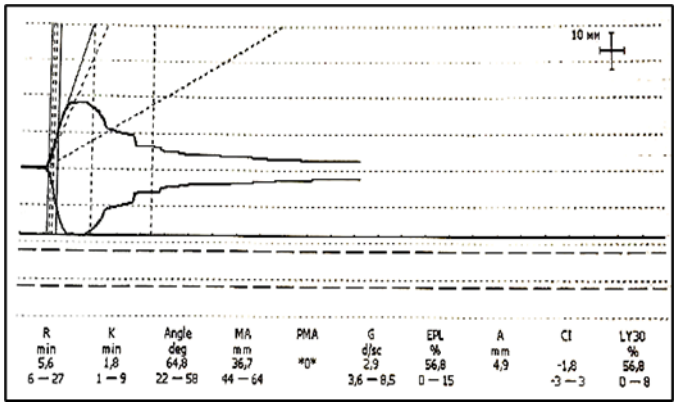

Figure 4: Clinical example of fibrinolysis activation during the transition from the hypercoagulable phase to the hypocoagulable phase of DIC on TEG (D-Dimer – 1150 µg/L, Antithrombin III – 75%).

The authors further examine the activation of neutrophil extracellular traps (NETs) as one of the pathophysiological causes of DIC in sepsis [7]. NETs release DNA with histones, neutrophil elastase, and cathepsin G to capture and destroy pathogens. It should be noted that elastase and cathepsin G are enzymes of the serine protease family. Subsequently, histones contribute to apoptosis of vascular endothelial cells and cause platelet aggregation [12]. Neutrophil elastase and cathepsin G degrade tissue factor pathway inhibitor (TFPI), which promotes thrombus formation [25]. If histones indeed induced apoptosis of vascular endothelial cells, as claimed by the authors, clinical symptoms of disseminated thrombus formation in the capillary network would not be observed, and hyperfibrinolysis would not be recorded. Increased bleeding would be attributed to a deficiency of factors VIII and von Willebrand, against the background of normal or slightly elevated levels of fibrin degradation products (FDP). To date, such data are absent in the literature.

However, if such information were to appear at some point, from a pathophysiological perspective, this would be a form of coagulopathy, but not disseminated intravascular coagulation (DIC). The authors also fail to consider the fact that NET activation occurs under the influence of superoxide radicals. Superoxide radicals bind to NO, forming a toxic substance — peroxynitrite.

The latter directly damages the vascular endothelium, leading to dysfunction. As a result, the blood coagulation system is activated, and clinical signs of the hypercoagulation phase of DIC emerge. Meanwhile, neutrophil elastase and cathepsin G, which are enzymes of the serine protease family, contribute not to thrombus formation, as the authors suggest, but rather to the enhancement of fibrinolysis processes.

Thus, the claim that activation of neutrophil extracellular traps (NETs) is one of the pathophysiological causes of DIC in sepsis does not fully correspond to reality.

On the Transfusion of Red Blood Cells or Whole "Warm" Blood in the Treatment of DIC

The authors of clinical guidelines mistakenly believe that failing to transfuse a sufficient amount of blood in severe hemorrhage caused by DIC will result in the patient's death. Hemic hypoxia cannot be a cause of DIC, unlike circulatory hypoxia, and patient death is a consequence of a deficiency in oxygen carriers. To date, there is no scientific study confirming that a patient died from hemic hypoxia. Furthermore, from a pathophysiological perspective, such scientific evidence is impossible due to the nature of massive blood loss. Massive bleeding can indeed lead to the development of DIC, but the mechanism is primarily due to circulatory hypoxia rather than hemic hypoxia [3]. Hemic and circulatory hypoxia are two different types of hypoxia. Misunderstanding this distinction leads to erroneous treatment strategies for DIC involving the transfusion of red blood cell components. Moreover, the unwarranted transfusion of red blood cell components or whole "warm" blood, which some clinicians have recently started to promote and implement, is not only extremely dangerous and harmful but also one of the causes of DIC.

On the Asymptomatic Type of DIC

According to the definition of DIC, the claim of an asymptomatic type, as referenced by the authors [50, 51], is pathophysiologically incorrect. The term "DIC" itself reflects its core nature - disseminated intravascular coagulation. Microthrombi form in almost all organs and tissues at the capillary level, which inevitably has a negative impact on the patient's clinical condition and laboratory results to some extent. For example, during the first phase of DIC (the hypercoagulable phase), patients exhibit clinical signs of DIC-related encephalopathy, cardiomyopathy, pneumonitis, liver function abnormalities, renal tubular dysfunction, and clinical signs of enteropathy and intestinal motility disorders. Therefore, it is incorrect to speak of an asymptomatic form of DIC.

On the other hand, there are patients with congenital or acquired hypercoagulable syndrome. In hypercoagulable syndrome, laboratory tests show reduced blood clotting time and prolonged fibrinolysis time. It is important to understand that, unlike the hypercoagulable phase of DIC, hypercoagulable syndrome can be clinically asymptomatic. It can be detected only through laboratory or instrumental methods for assessing the coagulation system. Undoubtedly, hypercoagulable syndrome increases the risk of developing DIC. The presence of hypercoagulable syndrome not only requires an expansion of methods for monitoring hemostatic parameters but also suggests a highly personalized approach to the prevention and treatment of DIC. In cases of acquired hypercoagulable syndrome, DIC prevention should focus on blocking or inhibiting the etiological factors that caused hypercoagulation, as well as creating adverse conditions for the development of the pathophysiological mechanisms of DIC.

It is likely that the authors referred to hypercoagulable syndrome, which indeed can be clinically asymptomatic. However, labeling it as an asymptomatic type of DIC or pre-DIC [23, 51] is incorrect and misleading for clinicians. Ultimately, this inaccuracy contributes to the development of erroneous approaches to the diagnosis, prevention, and treatment of DIC.

On Standards and Protocols for DIC Treatment

Clinicians must understand that standard methods for treating DIC do not exist and cannot exist due to objective reasons, despite the presence of continually updated protocols. There is only fundamental treatment principles based on a deep understanding of the mechanisms underlying coagulopathy. Treatment of DIC should be individualized for each clinical case, considering the etiology and pathogenesis of the coagulopathy, and should focus on comprehensive support of compensatory hemostatic mechanisms. Monitoring of hemostatic parameters should not rely on standard analytical schemes. It is important to consider only those parameters whose changes have clinical significance for the specific patient. Ignoring these principles and adhering to "blind" treatment standards objectively increases the risk of acute DIC transitioning into recurrent or chronic forms, which can lead to adverse outcomes.

DIC in Solid Tumors

There is evidence that patients with DIC caused by sepsis, hematologic malignancies, or obstetric conditions can be successfully treated for DIC, whereas DIC syndrome associated with solid cancer may not respond to standard treatment [18]. Unfortunately, the authors do not highlight the primary reasons underlying the complexity of such treatment, leading to the omission of key aspects of therapy. Clinicians must understand that, from a pathophysiological perspective, the complexity of treating DIC associated with solid tumors is primarily due to the following factors:

1. Some forms of cancer are capable of expressing procoagulant proteins such as tissue factor (TF), cysteine protease (CP), factor VII, procoagulant microparticles (MP), inflammatory cytokines, proangiogenic factors, and producing adhesive molecules that bind platelets, endothelial cells, and leukocytes either through the secretion of soluble factors or via direct adhesive contact [10, 24].
2. Overexpression of plasminogen activator inhibitor 2 (PAI 2) is observed in various tumor types. Plasminogen activator inhibitor 2 (PAI 2) is an important regulator of plasminogen activity.
3. Tumor cells secrete heparanase, which activates factor X and inactivates TF inhibitor [26]. From a pathophysiological perspective, these listed factors are key determinants in the specific treatment characteristics of DIC in solid tumors.

Mechanisms of DIC Formation and Its Difference from Thromboembolism

The formation of DIC is based on Virchow's triad: reduced blood flow velocity, endothelial dysfunction, and activation of the blood coagulation system. Any pathological condition that promotes the development of at least one of these factors can lead to the onset of DIC.

It is important not to confuse DIC with other coagulation system disorders, where either hypercoagulation or hypocoagulation initially predominates. This distinction is critically important, as many authors mistakenly equate DIC with isolated symptoms of increased bleeding or thrombosis. DIC is a pathological condition of the hemostatic system in which, in the early stages, a large number of microthrombi form in the capillaries of all organs and tissues. Ultimately, this leads to impaired tissue nutrition and the dysfunction of various organs.

Distinguishing DIC from Thromboembolic Disease. It is also important to differentiate DIC from thromboembolic disease. Unlike DIC, thromboembolism involves the formation of one or several clots in a specific area of blood circulation, typically not in the capillaries but in larger vessels.

Diagnosis of DIC: Proposed Criteria and Scoring System

Various clinical conditions can influence the laboratory parameters commonly used for diagnosing DIC. These parameters include general coagulation tests, platelet count, prothrombin time (PT), fibrinogen levels, and fibrin degradation products (FDP). To facilitate the diagnostic process for DIC, each of four different guidelines recommends using a scoring system

[8, 23, 45, 46]. The guidelines present three different diagnostic criteria, which include similar global coagulation tests, as established by ISTH/SSC [39], the Japanese Ministry of Health, Labour, and Welfare (JMHLW) [19], and the Japanese Association for Acute Medicine (JAAM) [13]. It has been reported that the JMHLW score correlates well with the severity of DIC and can be used to predict the outcome of the disease [50]. The ISTH overt DIC score is useful and specific for diagnosing DIC of both infectious and non-infectious etiologies [16, 14]. The JAAM score is sensitive for detecting septic DIC and correlates with the ISTH and JMHLW scores and the disease outcome [13, 16]. However, a prospective study conducted in Japan found no significant differences in the predictive odds for DIC outcomes among these three diagnostic criteria [36], suggesting that in addition to using scoring systems, the identification of hemostatic molecular markers and changes in global coagulation tests is necessary. Therefore, some authors confidently recommend using combinations of tests repeated over time in patients suspected of having DIC syndrome [6, 20, 40]. A template for a scoring system for non-overt DIC has been proposed, which includes global coagulation tests, changes in general coagulation tests, and hemostatic molecular markers [39, 41, 52]. The authors state that the bleeding type of DIC can be easily diagnosed using the ISTH overt-DIC criteria [39] and JMHLW [19], while the organ failure type of DIC is diagnosed according to the JAAM diagnostic criteria [13]. The massive bleeding type of DIC can be diagnosed using any of the three diagnostic criteria [13, 19, 39]; however, these criteria are insufficient for diagnosing the asymptomatic type of DIC. Diagnosing the asymptomatic type of DIC requires the use of hemostatic molecular markers [17].

It is evident that the presented information creates significant confusion among clinicians, primarily due to the lack of clarity regarding the practical significance and specificity of the proposed diagnostic criteria. The role of hemostatic molecular markers, which are supposed to complement the DIC scoring system, remains uncertain. Moreover, the scoring system for diagnosing DIC proposed by the authors raises concerns for objective reasons. Assessing the state of hemostasis solely based on coagulation tests is fundamentally impossible [4]. For example, diagnosing the hypercoagulable phase of DIC does not require coagulation data or platelet counts, as these parameters often do not correlate with the severity of the condition. The hypercoagulable phase of DIC manifests clinical signs of microcirculation disturbances in various organs and tissues from the early stages. Clinicians must understand that coagulation tests or specific blood coagulation markers are not necessary for diagnosing DIC phases [4]. Laboratory and instrumental methods for studying hemostasis are mainly required to monitor therapy effectiveness, adjust drug dosages, and select appropriate treatment methods. For diagnosing the phases of DIC, clinical data, blood clotting time by the Lee-White method, or TEG indicators are sufficient.

Laboratory Tests

According to the information presented in the referenced guidelines and publications, global coagulation tests are considered important for assessing the degree of activation and consumption of coagulation factors. However, the authors note that prothrombin time is prolonged in approximately 50% of patients with DIC [6]. Additionally, deviations in this parameter are also frequently observed in patients with liver disease or vitamin K deficiency. Therefore, the authors emphasize that a sensitive indicator of DIC is a decrease in platelet count or a clear trend towards a decrease [23].

This statement creates confusion, as a decrease in platelets can also be observed in patients with bone marrow disorders, antiphospholipid syndrome, microangiopathic hemolytic anemia, etc. This underscores the need for clarity for clinicians. It is important to understand that the causes of platelet count reduction in DIC and bone marrow disorders differ. Furthermore, in DIC, the laboratory decrease in platelet count may be minimal, but platelet function can be significantly impaired. For example, in acute promyelocytic leukemia, the platelet count may be over 80-100×10^9/L. However, the patient may clinically exhibit increased bleeding, and the hypocoagulable phase of DIC may be registered on TEG. In contrast, in aplastic thrombocytopenia, when the platelet count is 20-30×10^9/L, there may be no observed hemostatic disorders at all. Additionally, the authors do not take into account the existence of various types of thrombocytopathies, where the platelet count does not correlate with the severity of coagulopathy.

The next laboratory parameter for diagnosing DIC that the authors point out is a decrease in fibrinogen levels. They assert that its level is a valuable indicator for diagnosing DIC caused by leukemia or obstetric conditions. However, it is not observed in the majority of patients with septic DIC syndrome [23]. Authors of guidelines and scientific publications on the prevention and treatment of DIC should consider that fibrinogen levels are often not a reliable diagnostic indicator for this condition. For example, in acquired dysfibrinogenemia, which develops in cases of multiple organ failure, autoimmune and allergic diseases, hepatitis, sepsis, and other conditions, fibrinogen levels in the blood may remain normal or elevated despite clinical, laboratory, and instrumental signs of hypocoagulation. This is due to changes in the monomeric structure of the fibrinogen molecule that occur with dysfibrinogenemia. As a result, these monomers cannot polymerize into fully functional fibrin structures, which, in turn, suppresses platelet aggregation function.

The Role of Antithrombin III and Protein C in Diagnosing Disseminated Intravascular Coagulation (DIC)

The guidelines often cite scientific studies emphasizing that patients with DIC exhibit reduced levels of natural anticoagulants such as antithrombin (AT) and Protein C. This is indeed the case; however, it is important to note that it

is not DIC that causes their reduction, but rather the reduction in their activity that often leads to the development of DIC. The distinction between these formulations is significant and affects the choice of the appropriate prevention and treatment algorithms for DIC. Ultimately, this is confirmed by the authors of the guidelines and publications themselves. They note that DIC often resolves spontaneously with appropriate treatment of the underlying condition [1, 2, 5, 30, 31, 37, 43, 55].

Another inaccuracy in the formulation is that many authors emphasize the importance of determining antithrombin III (AT) activity to achieve the full effectiveness of unfractionated heparin [8, 22, 23, 45, 46]. This can mislead clinicians. Upon reading such information, clinicians may prefer low molecular weight heparins over unfractionated heparins for treating DIC. A small but important clarification is needed. The necessity of determining AT activity applies to all heparin-like drugs, including both unfractionated and low molecular weight heparins.

Assessment of ADAMTS13 Activity in Conjunction with Coagulation Profile

The guidelines and publications reviewed indicate that decreased ADAMTS13 activity and elevated levels of soluble thrombomodulin (TM), PAI-I, and von Willebrand factor are often observed in patients with disseminated intravascular coagulation (DIC) and have prognostic significance [11, 15, 54]. It has been shown that the biphasic waveform of activated partial thromboplastin time (APTT) is associated with DIC and apparently has positive prognostic value for the disease [9, 42]. Although many promising DIC markers have been reported, no single marker can be used alone for diagnosing DIC. Thus, the four guidelines mentioned above [8, 23, 45, 46] recommend that DIC should not be diagnosed based solely on the level of a single marker but rather on a combination of laboratory markers. Among the four types of DIC, important parameters for diagnosing DIC with massive bleeding include prothrombin time (PT), fibrinogen, and platelets, while for identifying the bleeding type of DIC, fibrinogen, FDP, and the plasminogen-plasmin inhibitor complex (PPIC) are crucial. Meanwhile, platelets, PT, and antithrombin (AT) are important for diagnosing the organ failure type of DIC, whereas hemostatic molecular markers such as soluble fibrin (SF) and the thrombin-AT complex are significant for diagnosing the asymptomatic type of DIC.

The combination of laboratory markers proposed by the authors for diagnosing DIC is of limited effectiveness and will inherently never fully reflect the true state of hemostasis. This issue is not related to the choice of specific laboratory markers. Coagulation profiles and platelet levels provide only a partial understanding of the potential of laboratory parameters to regulate the blood coagulation system. However, this does not mean that these parameters can effectively ensure hemostasis [4]. The authors focus primarily on finding a combination of key hemostasis laboratory markers. Unfortunately, this approach completely ignores the data from instrumental methods of hemostasis assessment. Unlike the combination of coagulation markers, instrumental methods allow not only a comprehensive objective evaluation of hemostasis in action but also separate assessments of the coagulation, anticoagulation, and fibrinolytic systems [4].

Additionally, it is important to note that the hemostasis markers proposed by the authors change not only in DIC. For instance, decreased ADAMTS13 activity, which the authors refer to in diagnosing DIC, also occurs in other coagulopathies. Examples include thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, Apshuz-Schulman syndrome, microangiopathic hemolytic anemia, and others. Therefore, these recommendations introduce discord in the clinical understanding of processes regulating hemostasis and create confusion in the diagnosis and monitoring of hemostatic status.

Key Approaches to the Treatment of DIC

This article does not aim to provide a detailed description of all possible treatment options for DIC. There can be numerous treatment options. It is important to understand that the choice of therapy, dosage, and number of medications must strictly adhere to the principles of a personalized approach. However, the fundamental approaches to DIC therapy remain unchanged and will be discussed further as primary tasks and priorities.

Unfortunately, in the reviewed recommendations and articles, the treatment strategy for DIC is often contradictory and based on incorrect assertions. For instance, all four guidelines [8, 23, 45, 46] emphasize that treating the underlying disorders is a cornerstone of DIC therapy. At the same time, they also note that, to date, there is no high-quality evidence supporting the effectiveness of treating the underlying disorder in patients with DIC.

Authors of the articles assert that DIC often resolves spontaneously with appropriate treatment of the underlying disease [1, 2, 5, 30, 31, 37, 43, 55]. This is difficult to disagree with. However, the phrase "appropriate treatment" is too general and does not provide specific recommendations for clinicians. Furthermore, unfortunately, the diagnosis, prevention, and treatment of DIC are often managed by non-specialist physicians (internists, cardiologists, surgeons, obstetricians-gynecologists, anesthesiologists, intensive care specialists, etc.). Even more concerning is the absence of clinical transfusion specialists among the authors of clinical guidelines and scientific articles. Ultimately, all these factors objectively contribute to the high mortality rate from DIC, which currently ranges from 45% to 78% [35].

Clinicians must understand that diagnosing, preventing, and treating DIC require not only skills in comprehensive analysis of indicators but also a personalized approach to each patient. Fundamental knowledge of the blood coagulation system, understanding of the pathophysiological mechanisms of hemostatic disorders, and the ability to analyze clinical, laboratory, and instrumental data are essential for timely diagnosis, effective prevention, and therapy of DIC.

Existing recommendations and protocols for the treatment of DIC primarily consist of a simple enumeration of methods and means for correcting hemostasis. All clinical guidelines for diagnosing and treating coagulopathies follow the same logical sequence - there is a patient with an underlying condition, associated pathology, clinical risk factors, recommended doses, and specific medications. However, this sequence omits two crucial elements as if they are irrelevant: the indicators of the vascular-platelet hemostasis that will be targeted by the therapy, and the absence of comprehensive monitoring and personalized dynamic assessment of the effectiveness of the therapy being conducted. It seems that the developers of clinical guidelines and protocols for using hemostasis-affecting medications assume by default that there is a standard hemostatic disturbance in all patients. Therefore, there is a somewhat averaged standard therapy with certain drug groups and dosages, which are expected to always have a positive effect on correcting the hemostatic system. Clearly, such logic is not only questionable but also harmful.

The recommended algorithm for DIC therapy should be based not on recommendations derived from contentious conclusions of statistical meta-analysis, subjective, and constantly changing treatment protocols, but on objective, fundamental knowledge of hemostasis system functioning, pharmacological mechanisms of drug action, a personalized approach to analyzing results from objective methods of assessing vascular-platelet hemostasis, and all involved systems. A misunderstanding of this principle leads to the authors' view that treating DIC is one of the cornerstones of ensuring hemostasis [17].

The primary task in treating DIC is to promptly identify pathologically altered hemostasis laboratory parameters, conduct a comprehensive assessment of hemostasis systems using instrumental methods, and perform dynamic monitoring of these parameters.

The second priority is to focus on treating the underlying disease that has caused or contributes to the development of DIC.

The third priority involves methods and approaches for correcting the blood coagulation system, taking into account a personalized approach and targeted intervention on key pathophysiological mechanisms of hemostatic disruption.

Blood Component Transfusion: Hemodilution and Coagulation Factor Deficiency

The issues concerning the appropriateness and safety of transfusing red blood cell components in the treatment of DIC were addressed earlier in the text.

Regarding platelets and plasma coagulation factors, a low level of platelets and coagulation factors, especially fibrinogen, can indeed increase the risk of bleeding. Thus, the guidelines [8, 23, 45, 46] recommend administering platelet concentrates (PC) and fresh frozen plasma (FFP) to patients with DIC who are experiencing active bleeding or who are at high risk of bleeding and require invasive procedures. This recommendation is difficult to disagree with. The effectiveness of plasma coagulation factors in FFP is indeed directly dependent on the functional state and quantity of platelets.

Regarding the Effect of Hemodilution and Coagulation Factor Deficiency in Acute Massive Hemorrhage

Hemodilution and coagulation factor deficiency do indeed occur. However, these factors are not the primary cause of increased bleeding in DIC, as many authors suggest. The minimally effective levels of each plasma coagulation factor vary. For example, the minimally effective level of factor VIII is 30-35%, factor VII is 5-7%, factor X is 10-15%, factor XIII is 2-5%, and fibrinogen (factor I) is 0.8 g/L, etc. Each factor has different conditions and rates of synthesis in the body, as well as varying half-lives. Most claims that DIC is caused by hemodilution and deficiency of plasma coagulation factors lack scientific evidence and are based only on theoretical considerations. This is due to objective reasons. In cases of acute massive hemorrhage and signs of DIC, clinicians do not measure all plasma coagulation factors. There is no clinical need for this. Moreover, if increased bleeding in DIC were solely due to hemodilution and coagulation factor deficiency, transfusion of FFP would quickly and effectively resolve the issue of the hypocoagulable phase of DIC. However, this is not observed in practice. Despite the administration of large volumes of FFP, the mortality rate from DIC remains high (45% to 78%) [35].

Thus, claims that increased bleeding in DIC is due to hemodilution or deficiency of plasma coagulation factors lack sufficient scientific support and clinical justification and can only be considered from a theoretical perspective.

Regarding platelet transfusion, the threshold for transfusing platelets depends on the clinical condition of the DIC patient. Typically, platelet concentrates (PC) are administered to patients with DIC who are experiencing active bleeding and have a platelet count ≤ 50 × 109/L. A much lower threshold of 10 to 20 × 109/L is used for patients without bleeding who develop DIC after chemotherapy. PC may be administered in higher concentrations to patients deemed at high risk of bleeding based on other clinical or laboratory indicators [44]. For transfusion of fresh frozen plasma (FFP), it is

recommended to use large volumes to correct coagulation defects associated with prolonged APTT or prothrombin time (more than 1.5 times the normal level) or decreased fibrinogen levels (less than 0.8 g/L). Some authors suggest starting with an initial dose of 15 ml/kg of FFP [17].

In all clinical guidelines and scientific works, the dosage of fresh frozen plasma (FFP) is calculated in ml/kg. It is important to note that the volume of FFP transfusion should be specified not in ml/kg of body weight but in whole doses (0.06 doses/kg), with the number of whole doses being minimized. This is because prescribing FFP in ml/kg often leads to an increased number of doses administered. Conversely, increasing the number of transfusions of heterogeneous doses of FFP raises the risk of post-transfusion complications: volume overload, TRALI syndrome, urticaria, alloimmunization to plasma proteins, etc. For example, if the calculated volume of FFP based on the patient's weight is 1125 ml, this roughly equals 4.6 doses. Therefore, 0.6 of a dose amounts to the fifth bag of heterogeneous FFP. This raises a legitimate question about the clinical necessity of transfusing the fifth bag of FFP. Considering that the effectiveness of the transfused FFP is monitored through hemostasis data, a more justified and safer approach would be to administer 4 doses of FFP. After the fourth dose, it will be necessary to monitor hemostasis parameters and decide whether to continue FFP transfusion. This approach is supported by the recommendations from the authors of the provided guidelines regarding the need to prevent volume overload by transfusing prothrombin complex concentrate instead of FFP [8, 17, 23, 45, 46].

Fibrinogen deficiency associated with massive bleeding in DIC can be corrected with the administration of purified fibrinogen concentrates or cryoprecipitate [17]. Clinicians should be aware that the transfusion of cryoprecipitate is not calculated in ml/kg, as indicated by the authors of guidelines and articles [8, 17, 23, 45, 46], but in doses. This is because the fibrinogen content in one dose varies among different manufacturers. Additionally, one dose of cryoprecipitate may correspond to a volume ranging from 15 to 30 ml. Therefore, the calculation of the number of doses of cryoprecipitate depends on the fibrinogen content in one dose as specified by the manufacturer. Clinicians should also be aware that, in addition to fibrinogen, cryoprecipitate contains coagulation factors VIII and XIII.

Use of "bypass" Hemostatic Agents: Indications and Limitations

In the mentioned treatment guidelines, the authors note that the efficacy and safety of recombinant factor VIIa in DIC and life-threatening bleeding have not been established. Therefore, its use is recommended with caution or within the framework of clinical trials.

However, it should be noted that the authors' recommendations for the use of "bypass" hemostatic agents in the treatment of DIC do not align with the pathophysiology of this condition and are incorrect. Furthermore, the authors do not consider that effective use of "bypass" hemostatic agents requires the following conditions to be met: correction of metabolic acidosis, hypofibrinogenemia, thrombocytopenia, and hyperfibrinolysis. Therefore, these agents are appropriate for stopping bleeding in hemophilia, von Willebrand disease, and other coagulation disorders, but not for treating DIC and life-threatening bleeding.

Key Points on the Use of Unfractionated and Low-Molecular-Weight Heparins in DIC Therapy

The use of anticoagulant therapy is a rational approach based on the understanding that DIC is characterized by extensive activation of coagulation. There are several differences in the recommendations for the use of heparin in patients with DIC among the four guidelines [8, 23, 45, 46]. The authors of the guidelines indicate that therapeutic doses of heparin should be considered in cases of DIC where thrombosis predominates [28, 33]. However, other authors argue the opposite, citing an experimental study [27] that states the use of heparin to suppress coagulation activation in DIC does not lead to improved clinically significant outcomes. A recent large study of patients with severe sepsis demonstrated a modest benefit of low-dose heparin on 28-day mortality and emphasized the importance of not discontinuing heparin treatment in patients with DIC syndrome and abnormal coagulation parameters [22].

In the provided guidelines, the use of heparin is not recommended for patients with bleeding or massive bleeding in DIC due to the increased risk of hemorrhage. However, it is recommended for patients with asymptomatic DIC to prevent the onset of deep vein thrombosis. Opposing views on this issue are abundant in articles, guidelines, and treatment protocols, causing discord in DIC treatment methods and leading to numerous discussions and debates among clinicians.

Many authors in their scientific publications assert the clinical advantage of low-molecular-weight heparins over unfractionated heparins in the treatment of DIC [17, 21, 22, 32]. This advantage is also mentioned in many DIC and massive bleeding treatment protocols [8, 23, 45, 46]. The inaccuracies in the conclusions of such publications can be attributed to the insufficient qualifications of the reviewers of the scientific journals in which these articles and treatment protocols were published. Clinicians should be aware that, in the treatment of DIC and acute massive bleeding, the use of low-molecular-weight heparins does not offer advantages over unfractionated heparins. Moreover, their use in this context is unjustified and potentially dangerous for the patient.

First, it is important to note that the list of indications, contraindications, and major side effects for heparin-like drugs is the same.

Regarding their points of action: Unfractionated heparins inhibit both factor Xa and factor IIa equally, while low-molecular-weight heparins primarily inhibit factor Xa. This fact is crucial in determining the differences in laboratory monitoring of the effectiveness and adequacy of heparin use. For monitoring the dose and effectiveness of unfractionated heparins, standard coagulation tests (e.g., activated partial thromboplastin time - APTT) are sufficient. However, for monitoring the dose and effectiveness of low-molecular-weight heparins, it is essential to measure Anti-Xa activity. Unfortunately, not all clinicians are aware of this. Furthermore, not all clinical laboratories have the capability to measure Anti-Xa activity. Many authors in their scientific studies evaluate the clinical effectiveness of low-molecular-weight heparins without considering Anti-Xa activity, which is incorrect.

Second, it should be noted that, unlike unfractionated heparins, low-molecular-weight heparins are not only very difficult to use in the treatment of DIC but also potentially dangerous. This is because their use excludes the possibility of dose titration. This issue is particularly relevant when dosing anticoagulants during the hypocoagulable phase (the appropriateness and necessity of using direct anticoagulants during the hypocoagulable phase of DIC will be discussed later). This is crucial as the enzymatic processes involved in maintaining hemostasis are rapid, and their intensity changes continuously during intensive therapy. As a result, the risk of ineffectiveness and danger of DIC therapy with low-molecular-weight heparins significantly increases. This last fact is a major and objective drawback of using low-molecular-weight heparins.

Thus, the advantages of using unfractionated heparins over low-molecular-weight heparins in the treatment of various coagulopathies, including DIC, are evident:

1. Unfractionated Heparins:

- Allow flexible dose titration based on the clinical situation, which is important in the treatment of DIC.
- Have the capability for reversible action if needed (using protamine).
- Can be used to control both thrombogenesis and hypercoagulation.

2. Low-Molecular-Weight Heparins:

- Have more predictable pharmacokinetics but require strict and specific monitoring, as their action is difficult to regulate.
- Their use is limited in DIC conditions due to the lack of precise dose titration.
- Can be potentially dangerous when used during the hypercoagulable phase of DIC, as the risk of bleeding is higher due to inadequate dose control.

Given the above, the use of unfractionated heparins is preferable in the therapy of DIC, especially when flexible dose adjustment is needed in response to changes in the patient's condition.

On the Appropriateness and Necessity of Using Direct Anticoagulants During the Hypocoagulable Phase of DIC

The use of direct anticoagulants during the hypercoagulable phase of DIC is generally not questioned by clinicians. However, their application during the hypocoagulable phase remains controversial and is the subject of much discussion. To clarify this issue, it is important to recall that the hypocoagulable phase of DIC is not so much caused by hemodilution and a reduction in coagulation factors as it is by the high levels of fibrin degradation products (FDP) in the blood. These FDP inhibit the polymerization of fibrin monomers and impair platelet function. The removal of FDP from the body occurs through phagocytosis. The primary cause of the hypocoagulable phase of DIC is the imbalance between the rate of fibrin degradation product formation and the body's ability to eliminate them.

Thus, from a pathophysiological perspective, therapy for the hypocoagulable phase of DIC syndrome should aim, on one hand, to inhibit hyperfibrinolysis, which is clinically achieved through the use of lysine-containing amino acids and protease inhibitors. On the other hand, the treatment should control the rate and amount of thrombus formation. This is achieved by transfusing large volumes of FFP in combination with anticoagulants. It is important to note that, in this case, the dose of the prescribed anticoagulant should be significantly lower than the dose recommended for the hypercoagulable phase. The use of short-acting anticoagulants (unfractionated heparins) and comprehensive dynamic monitoring of hemostatic parameters is not only a mandatory requirement for effective DIC therapy but also an important condition for restoring the balance between the coagulation and anticoagulation systems of the blood.

Conclusion

The identified conceptual errors in the presented guidelines and publications lead to false principles in the diagnosis, prevention, and treatment of DIC. A deep understanding of the functioning of the coagulation system is crucial for accurately assessing its condition and selecting the most effective therapy. The principles of diagnosing, preventing, and treating DIC should be based on the pathophysiological mechanisms of coagulopathy, clinical data, laboratory and instrumental methods of investigation, as well as an understanding of the mechanisms of therapeutic agents with a

personalized approach. Only a specialist in clinical transfusiology can provide the appropriate professional knowledge on this topic, and only a clinical transfusiologist can offer effective hemostatic correction in cases of DIC.

References

1. Abraham E, Laterre PF, Garg R, Levy H, Talwar D. et al. (2005). Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med*, 353:1332-1341.
2. Abraham E, Reinhart K, Svoboda P, Seibert A, Olthoff D.et al. (2001). Assessment of the safety of recombinant tissue factor pathway inhibitor in patients with severe sepsis: a multicenter, randomized, placebo-controlled, single-blind, dose escalation study. *Crit Care Med*, 29:2081-2089.
3. Belousov A. (2018). Current Faults and Recommendations for Transfusion of Red Blood Cell Assessment and Clinical Evaluation of Changes in Hematocrit. *Am J Anesth Clin Res*, 4(1):001-007.
4. Belousov A. (2024). Modern strategies of anticoagulant and antiplatelet therapy: Novel approaches to diagnosing the hemostatic system using laboratory and instrumental methods. *Journal of Vascular Medicine & Surgeries*, 2(1):1-8.
5. Bernard GR, Vincent JL, Laterre PF, LaRosa SP, Dhainaut JF. Et al. (2001). Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*, 344:699-709.
6. Bick R. (1996). Disseminated intravascular coagulation: objective clinical and laboratory diagnosis, treatment, and assessment of therapeutic response. *Semin Thromb Hemost*, 22:69-88.
7. Brinkmann V, Reichard U, Goosmann C, Fauler B, Uhlemann Y.et al. (2004). Neutrophil extracellular traps kill bacteria. *Science*, 303:1532-1535.
8. Di Nisio M, Baudo F, Cosmi B, D'Angelo A, De Gasperi A. et al. (2012). Italian Society for Thrombosis and Haemostasis Diagnosis and treatment of disseminated intravascular coagulation: guidelines of the Italian society for haemostasis and thrombosis (SISET) Thromb Res, 129:e177-e184.
9. Downey C, Kazmi R, Toh CH. (1998). Early identification and prognostic implications in disseminated intravascular coagulation through transmittance waveform analysis. *Thromb Haemost*, 80:65-69.
10. Falanga A, Marchetti M, Vignoli A. (2013). Coagulation and cancer: biological and clinical aspects. *J Thromb Haemost*,11(2):223-233.
11. Faust SN, Levin M, Harrison OB, Goldin RD, Lockhart MS. Et al. (2001). Dysfunction of endothelial protein C activation in severe meningococcal sepsis. *N Engl J Med*, 345:408-416.
12. Fuchs TA, Brill A, Duerschmied D, Schatzberg D, Monestier M. et al. (2010). Extracellular DNA traps promote thrombosis. *Proc Natl Acad Sci U S A*, 107:15880-15885.
13. Gando S, Iba T, Eguchi Y, Ohtomo Y, Okamoto K. et al. (2006). Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group A multicenter, prospective validation of disseminated intravascular coagulation diagnostic criteria for critically ill patients: comparing current criteria. *Crit Care Med*, 34:625-631.
14. Gando S, Wada H, Asakura H, Iba T, Eguchi Y. et al. (2005). Evaluation of new Japanese diagnostic criteria for disseminated intravascular coagulation in critically ill patients. *Clin Appl Thromb Hemost*, 11:71-76.
15. Habe K, Wada H, Ito-Habe N, Hatada T, Matsumoto T. et al. (2012). Nobori T. Plasma ADAMTS13, von Willebrand factor (VWF) and VWF propeptide profiles in patients with DIC and related diseases. *Thromb Res*, 129:598-602.
16. Hatada T, Wada H, Nobori T, Okabayashi K, Maruyama K. et al. (2005). Plasma concentrations and importance of high mobility group box protein in the prognosis of organ failure in patients with disseminated intravascular coagulation. *Thromb Haemost*, 94:975-979.
17. Hideo Wada, Takeshi Matsumoto, Yoshiki Yamashita. (2014). Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. *J Intensive Care*, 2(1):15.
18. Kawasugi K, Wada H, Hatada T, Okamoto K, Uchiyama T. et al. (2011). Japanese Society of Thrombosis Hemostasis/DIC subcommittee Prospective evaluation of hemostatic abnormalities in overt DIC due to various underlying diseases. *Thromb Res*.128:186-190.
19. Kobayashi N, Maegawa T, Takada M, Tanaka H, Gonmori H. (1983). Criteria for diagnosis of DIC based on the analysis of clinical and laboratory findings in 345 DIC patients collected by the research committee on DIC in Japan. *Bibl Haemotol*, 49:265-275.
20. Levi M, Ten Cate H. (1999). Disseminated intravascular coagulation. *N Engl J Med*, 341:586-592.
21. Levi M, Opal SM. (2006). Coagulation abnormalities in critically ill patients. *Crit Care*, 10:222.
22. Levi M, Levy M, Williams MD, Douglas I, Artigas A. et al. (2007). Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated) Am J Respir Crit Care Med. 176:483–490.

23. Levi M, Toh CH, Thachil J, Watson HG. (2009). Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol*, 145:24-33.
24. Magnus N, D'Asti E, Meehan B. et al. (2014). Oncogenes and the coagulation system-forces that modulate dormant and aggressive states in cancer. *Thromb Res*, 133(Suppl 2): S1-S9.
25. Massberg S, Grahl L, von Bruehl ML, Manukyan D, Pfeiler S. et al. (2010). Engelmann B. Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. *Nat Med*, 16:887-896.
26. Nadir Y, Brenner B. (2014). Heparanase multiple effects in cancer. *Thromb Res*, 133 (Suppl. 2): S90-4.
27. Pernerstorfer T, Hollenstein U, Hansen J, Knechtelsdorfer M, Stohlawetz P. et al. (1999). Jilma B. Heparin blunts endotoxin-induced coagulation activation. *Circulation*,100:2485-2490.
28. Patel R, Cook DJ, Meade MO, Griffith LE, Mehta G.et al. (2005). Burden of illness in venous thromboembolism in critical care: a multicenter observational study. *J Crit Care*, 20:341-347.
29. Prisco D, Paniccia R, Bonechi F, Francalanci I, Abbate R. et al. (1989). Evaluation of new methods for the selective measurement of fibrin and fibrinogen degradation products. *Thromb Res*, 56:547-551.
30. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS.et al. (2012). PROWESS-SHOCK Study Group Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med*, 366:2055-2064.
31. Saito H, Maruyama I, Shimazaki S, Yamamoto Y, Aikawa N.et al. (2007). Efficacy and safety of recombinant human soluble thrombomodulin (ART-123) in disseminated intravascular coagulation: results of a phase III, randomized, double-blind clinical trial. *J Thromb Haemost*, 5:31-41
32. Sakuragawa N, Hasegawa H, Maki M, Nakagawa M, Nakashima M. (1993). Clinical evaluation of low-molecular-weight heparin (FR-860) on disseminated intravascular coagulation (DIC); a multicenter co-operative double-blind trial in comparison with heparin. *Thromb Res*, 72:475-500.
33. Samama MM, Cohen AT, Darmon JY, Desjardins L, Eldor A. et al. (1999). Weisslinger N. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients; prophylaxis in medical patients with enoxaparin study group. *N Engl J Med*, 341:793-800.
34. Shorr AF, Trotta RF, Alkins SA, Hanzel GS, Diehl LF. (1999). D-dimer assay predicts mortality in critically ill patients without disseminated intravascular coagulation or venous thromboembolic disease. *Intens Care Med*, 25:207-210.
35. Solanki D, Lal D, Sunny A, et al. (2022). Temporal Trends, Predictors, and Outcomes of Disseminated Intravascular Coagulation in Hospitalizations with Sepsis. *Cureus* ,14(7): e27477.
36. Takemitsu T, Wada H, Hatada T, Ohmori Y, Ishikura K, Nobori T. et al. (2011). Prospective evaluation of three different diagnostic criteria for disseminated intravascular coagulation. *Thromb Haemost*, 105:40-44.
37. Tallman MS, Andersen JW, Schiffer CA, Appelbaum FR, Feusner JH. Et al. (2002). All-trans retinoic acid in acute promyelocytic leukemia: long-term outcome and prognostic factor analysis from the North American intergroup protocol. *Blood*, 100:4298-4302.
38. Tallman MS, Lefèbvre P, Baine RM, Shoji M, Cohen I. et al. (2004). Effects of all-trans retinoic acid or chemotherapy on the molecular regulation of systemic blood coagulation and fibrinolysis in patients with acute promyelocytic leukemia. *J Thromb Haemost*, 2:1341-1350.
39. Taylor FB, Toh CH, Hoots WK, Wada H, Levi M. (2001). Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*, 86:1327-1330.
40. Toh CH, Dennis M. (2003). Disseminated intravascular coagulation, old disease, new hope. *BMJ*, 327:974-977.
41. Toh CH, Hoots WK. (2007). The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview. *J Thromb Haemost*, 5:604-606.
42. Toh CH, Samis J, Downey C, Walker J, Becker L. et al. (2002). Biphasic transmittance waveform in the APTT coagulation assay is due to the formation of a Ca (++)- dependent complex of C-reactive protein with very-low-density lipoprotein and is a novel marker of impending disseminated intravascular coagulation. *Blood*, 100:2522-2529.
43. Vincent JL, Ramesh MK, Ernest D, Larosa SP, Pachl J.et al. (2013). A randomized, double-blind, placebo-controlled, phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. *Crit Care Med*, 41:2069-2079.
44. Wada H. (2004). Disseminated intravascular coagulation. *Clin Chim Acta*, 344:13-21.
45. Wada H, Asakura H, Okamoto K, Iba T, Uchiyama T. et al. (2010). Japanese Society of Thrombosis Hemostasis/DIC subcommittee Expert consensus for the treatment of disseminated intravascular coagulation in Japan. *Thromb Res*.125:6-11.

46. Wada H, Thachil J, Di Nisio M, Mathew P, Kurosawa S. et al. (2013). The Scientific Standardization Committee on DIC of the International Society on Thrombosis Haemostasis Guidance for diagnosis and treatment of DIC from harmonization of the recommendations from three guidelines. *J Thromb Haemost*, 11:761-767.
47. Wada H, Matsumoto T, Hatada T. (2012). Diagnostic criteria and laboratory tests for disseminated intravascular coagulation. *Expert Rev Hematol*, 5:643-652.
48. Wada H, Tamaki S, Tanigawa M, Takagi M, Deguchi A.et al. (1991). Plasma level of IL-1β in disseminated intravascular coagulation. *Thromb Haemost*, 65:364-368.
49. Wada H, Ohiwa M, Kaneko T, Tamaki S, Tanigawa M. et al. (1991). Plasma level of tumor necrosis factor in disseminated intravascular coagulation. *Am J Hematol*, 37:147-151.
50. Wada H, Wakita Y, Nakase T, Shimura M, Hiyoyama K. et al. (1995). Outcome of disseminated intravascular coagulation in relation to the score when treatment was begun. *Thromb Haemost*, 74:848-852.
51. Wada H, Minamikawa K, Wakita Y, Nakase T, Kaneko T.et al. (1993). Hemostatic study before onset of disseminated intravascular coagulation. *Am J Hematol*, 43:190-194.
52. Wada H, Hatada T, Okamoto K, Uchiyama T, Kawasugi K. et al. (2010). Japanese Society of Thrombosis Hemostasis/DIC subcommittee Modified non-overt DIC diagnostic criteria predict the early phase of overt-DIC. *Am J Hematol*, 85:691-699.
53. Wada H, Sakuragawa N. (2008). Are fibrin-related markers useful for the diagnosis of thrombosis? Semin Thromb Hemost. 34:33-38.
54. Wada H, Mori Y, Shimura M, Hiyoyama K, Nakasaki T. et al. (1998). Poor outcome in disseminated intravascular coagulation or thrombotic thrombocytopenic purpura patients with severe vascular endothelial cell injuries. *Am J Hematol*,58:189-194.
55. Warren BL, Eid A, Singer P, Pillay SS, Carl P. et al. (2001). Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA*, 286:1869-1878.