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REVIEW

Pathogenesis and management of sepsis patients with disseminated intravascular coagulation

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Abstract

Sepsis is a life-threatening organ dysfunction caused by dysregulation of the body's response to infection, and is one of the leading causes of death in intensive care units. In sepsis, the systemic inflammatory reaction that occurs activates the coagulation system and increases the consumption of clotting factors, leading to a serious complication of coagulopathy known as disseminated intravascular coagulation (DIC). DIC is a clinicopathological syndrome that is a complication of various diseases characterized by the activation of systemic blood coagulation and intravascular fibrin production, which can cause thrombosis of small- and medium-sized blood vessels and can even cause organ function failure along with the consumption of platelets and coagulation factors, resulting in a clinical picture of bleeding. In 35% of severe sepsis cases, and in shock sepsis DIC causes high mortality, which is associated with increased severity of illness and serious organ failure with poor outcomes. This article aims to summarize the evolving understanding of DIC pathogenesis in patients with sepsis and its implications for current and future management strategies.

Keywords: disseminated intravascular coagulation, pathogenesis, sepsis patients with DIC, sepsis, DIC management

Introduction

Sepsis is a serious and common disorder and the leading cause of death in non-coronary intensive care units worldwide. Sepsis is a clinical syndrome characterized by a dysregulated systemic response to infection due to inflammation. Systemic responses include fever, tachycardia, tachypnea, hypotension, and leukocytosis, which if not treated promptly can lead to multiple organ failure (MMOF).

Sepsis is often complicated by complications that worsen the prognosis, such as hemostasis disorders in the form of thrombocytopenia, coagulation disorders, and more complex ones such as Disseminated Intravascular Coagulation (DIC). DIC is defined as a clinicopathological syndrome that arises because it is triggered by other diseases that precede it and is characterized by excessive activation of the coagulation process, accumulation of fibrin in small or medium blood vessels, and the use of coagulation factors and platelets that exceed their production limits, triggering bleeding.

Epidemiologically, the incidence of DIC in cases of severe sepsis is found to be approximately 14–32%, even in cases of severe sepsis, and the incidence of DIC increased two decades ago to 35%. DIC due to sepsis can occur in any age, race, or sex. The overall mortality rate of children with sepsis-related DIC is 13-40%. This increased mortality rate is closely related to the severity which depends on the severity of the coagulopathy, the underlying condition, and the incidence of MOF. Therefore, it is important to review the information available in the literature on the approach and management in sepsis. This article summarizes the current and future developments in the pathogenesis and management of DIC in patients with sepsis.

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Discussion

Sepsis and Sepsis Shock

According to the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock 2016, sepsis is a life-threatening organ dysfunction caused by dysregulation of the body's systemic response to infection. Clinically, it can be explained that organ dysfunction is when there is an increase in the sequential organ failure assessment (SOFA) score of > 2 points or more which is associated with an increased risk of death in the hospital..[1,2]

Sepsis, if not recognized early and managed as soon as possible, can lead to septic shock, a condition of sepsis accompanied by persistent hypotension that requires vasopressors to obtain a MAP of 65 mmHg and serum lactate levels > 2 mmol/L (18 mg/dL) after adequate volume resuscitation. Sepsis shock is characterized by cellular dysfunction due to metabolic disturbances, severe circulatory disorders, unstable hemodynamics, multi-organ dysfunction, coagulopathy, and a high risk of death. For this reason, sepsis is a serious global health problem and is often found to be one of the major causes of death in critical care patients in intensive care units because it kills millions of people every year.[1]

Definition of DIC

Disseminated Intravascular Coagulation (DIC) is a clinicopathological syndrome that is a complication of various diseases characterized by activation of systemic blood coagulation and intravascular fibrin production, which can cause thrombosis of small- and medium-sized blood vessels, and can even cause organ function failure along with platelet consumption and coagulation factors, resulting in a clinical picture of bleeding.[3–5]

The Scientific and Standardization Committee (SSC) on DIC subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) defines DIC as an acquired syndrome characterized by intravascular coagulation with loss of integrity of the vascularization of the affected vasculature, originating from small vessels, arising from a variety of causes that, if exacerbated, can lead to organ dysfunction.[2,4,5] DIC can result from complications, such as infection, malignant processes of solid tumors, hematological malignancies, obstetric diseases, trauma, aneurysms, and liver disease. Diagnosis and treatment must also consider the underlying etiological conditions.[6,7]

There are two types of DIC: acute and chronic DIC. The acute type is characterized by massive and excessive activation of the fibrinolytic and anticoagulant systems. Acute DIC develops when large amounts of procoagulants (tissue factors) enter circulation over a short period of time (several hours to several days). Acute DIC requires the body's enormous ability to form coagulation factors, which predispose patients to the onset of bleeding. Acute DIC can occur in cases of endotoxin, extensive tissue trauma, preeclampsia complications in pregnant women, or detachment of placental tissue. Acute DIC also occurs in patients with hypotension or shock of various causes (e.g., surgery, extensive stroke, or heart attack).[6,7]

The chronic DIC type of coagulation activation is not as intense as the acute type; the amount of tissue factor is smaller, so the stimulation of the coagulation system is less intense and allows the body to compensate for the use of coagulation proteins and platelets. Chronic DIC usually develops slowly from weeks to months, with clinical manifestations being more thrombotic in nature. Chronic DIC is common in cancer, aortic aneurysms, and chronic inflammatory diseases. Important risk factors for cancer include advanced age, male sex, advanced stage, and necrosis of the tumor. Most chronic DIC occurs in patients with lung, breast, prostate, or colorectal adenocarcinomas.[6,7]

Sepsis with DIC

Infection, particularly septicemia, is the most common clinical condition that leads to DIC. Although all microorganisms can cause DIC, bacteria are the most common pathogens. DIC can occur in 30-50% of patients who develop sepsis due to gram-negative bacteria. Systemic infections by fungi or parasites can also cause DIC complications. For example, severe parasitic infections such as *P. falciparum* malaria are closely associated with the incidence of DIC and increased mortality. In general, the mechanism that occurs in the DIC process of patients with sepsis is different from that of leukemia or solid tumors.[2,8]

Sepsis and septic shock are caused by the systemic inflammatory response to infection. The clinical manifestations of DIC in sepsis are not caused by invading pathogens but rather by complications caused by sepsis, such as hypotension, coagulopathy, and multiorgan dysfunction, which lead to impaired regulation of inflammatory mediators in the host. One of the complications of sepsis that worsens the prognosis is impaired hemostasis in the form of thrombocytopenia, coagulation abnormalities, and more complex complications such as DIC[9,10] as shown in figure 1.

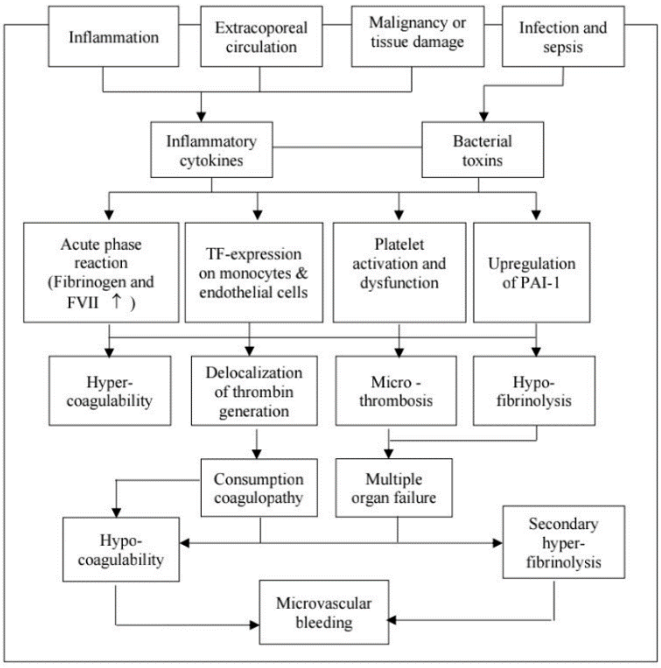

Figure 1. Etiology and course of DIC
DIC is mainly caused by inflammation, organ/tissue damage, infection, and sepsis, resulting in microthrombosis, multiple organ failure, and microvascular hemorrhage.[7]

Rangel-Frausto et al. reported a gradual increase in the frequency of disseminated intravascular coagulation (DIC) complications corresponding to the escalating severity of sepsis. Recent reports from Japan also indicate that DIC can be observed in approximately half of the patients with sepsis and septic shock admitted to intensive care units.[11] Furthermore, these reports that mortality rates in septic patients with DIC are significantly higher compared to overall septic patients without DIC.

Untreated DIC can lead to excessive thrombus formation within blood vessels, inevitably resulting in organ failure. This organ dysfunction further accelerates mortality.[10] Overall mortality rates for sepsis-associated DIC in children range from 13% to 40%, with reported incidence exceeding 90% in developing countries. However, data on the prevalence and incidence of DIC in Indonesia remain limited.[8]

Epidemiology

Epidemiologically, sepsis is the second leading cause of death in non-cardiac intensive care units and ranks among the top ten causes of death worldwide. The incidence of sepsis, based on the International Classification of Diseases, varies globally between 132 and 300 per 100,000 individuals annually. According to a 2010 bulletin published by the World Health Organization (WHO), sepsis is a primary cause of death in intensive care units in developed countries such as the United States, with approximately 750,000 cases reported each year and a sepsis prevalence rate of 3 cases per 1,000 people. Advances in pharmacotherapy and supportive care have improved survival rates; however, mortality ranges from 25% to 30% for severe sepsis and from 40% to 70% for septic shock, with these rates expected to rise with increasing age.[12]

Organ dysfunction is a cumulative effect that contributes to mortality. The mortality rate for sepsis patients without organ dysfunction is 15%, whereas the rate for those with organ dysfunction is 70%, despite advancements in critical care over recent decades. The importance of understanding sepsis epidemiology lies in its potential to drive progress in accurate diagnosis, treatment administration, and the prevention and management of sepsis-related complications.

Pathogenesis

The pathogenesis of sepsis is closely related to the causative agent and the resulting inflammatory response, which drives fibrin formation and deposition through simultaneous and continuous mechanisms, including: upregulation of procoagulant pathways, downregulation of physiological anticoagulants, suppression of fibrinolysis, and inflammatory consequences.[3]

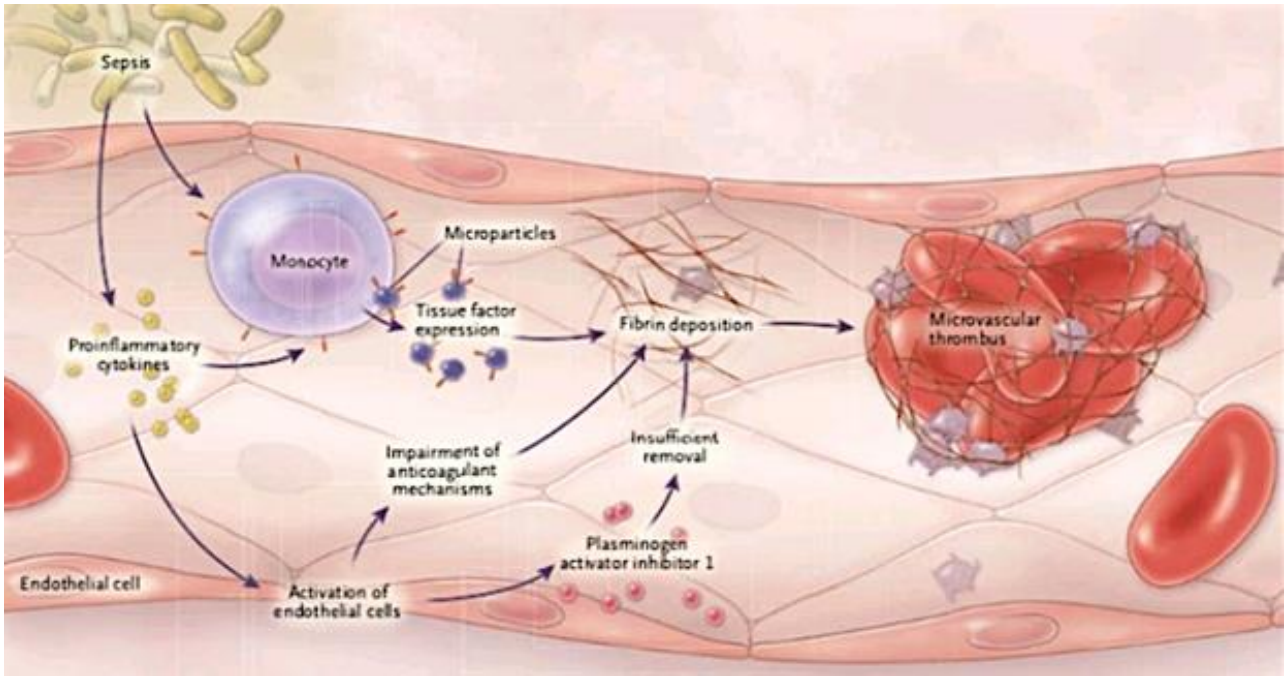

Figure 2. Pathogenesis of Sepsis-Associated Disseminated Intravascular Coagulation (DIC)[13]

In sepsis-associated disseminated intravascular coagulation (DIC), concurrent and simultaneous hematological derangements encompass four key mechanisms: (1) coagulation activation, mediated by tissue factor, leading to endothelial damage and thrombin generation; (2) impairment of physiological anticoagulant mechanisms, including suppression of the antithrombin system, attenuation of the protein C system, thereby failing to counterbalance thrombin formation, and reduced secretion of tissue factor pathway inhibitor (TFPI) by endothelial cells; (3) suppression of the fibrinolytic system due to the release of plasminogen activator inhibitor-1 (PAI-1) by endothelial cells as a consequence of bacteremia and endotoxemia; and (4) activation of inflammation.[3,9,10,14,15]

Tissue factor (TF)-mediated thrombin generation

Thrombin can be detected in circulation within 3–5 hours following bacteremia or endotoxemia. Ample scientific evidence demonstrates the crucial role of the tissue factor/factor VIIa system in initiating thrombin formation. Factor VIIa is known to be a key mediator of intravascular coagulation in sepsis. Inhibition of the factor VIIa pathway in sepsis can prevent the progression of disseminated intravascular coagulation (DIC), whereas inhibition of alternative pathways has not been shown to significantly affect the coagulation process.

Exposure to tissue factor (TF) in the circulation results from endothelial damage, tissue injury, inflammation, or tumor cells that can express procoagulant molecules (including TF). TF activates coagulation through the extrinsic pathway, where the TF-VIIa complex activates thrombin, which subsequently cleaves fibrinogen into fibrin and simultaneously induces platelet aggregation. However, the intrinsic pathway can also be activated in DIC, and activation of this pathway can further destabilize hemodynamics, potentially leading to hypotension.

Tissue factor is expressed on the surface of endothelial cells, monocytes, and platelets when these cells are stimulated by toxins, cytokines, or other mediators. The presence of endotoxins leads to an increase in several pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6. The cytokine IL-6 is the pro-inflammatory cytokine most strongly associated with the clinical manifestations of sepsis and its complications.

TF-mediated thrombin generation is a critical step in the pathogenesis of sepsis. Physiologically, this formation is promptly inhibited by antithrombin; however, with rapid thrombin generation, this inhibitory pathway can become overwhelmed, leading to thrombinemia. Circulating thrombin cleaves fibrinogen into

fibrin monomers. Thrombin also stimulates platelet aggregation, activates factors V and VIII, and releases plasminogen activator, which forms plasmin. Plasmin then degrades fibrin, producing fibrin degradation products, and further activates factors V and VIII. Excessive thrombin activity results in decreased fibrinogen, thrombocytopenia, consumption of coagulation factors, and fibrinolysis, leading to diffuse bleeding. Furthermore, the polymerization product of fibrinogen, fibrin clots, is deposited in the microcirculation. This fibrin deposition causes organ dysfunction.

Dysfunction of anticoagulant mechanisms

Antithrombin system — Thrombin formation is normally tightly regulated through various homeostatic mechanisms. However, once intravascular coagulation is initiated, these mechanisms become overwhelmed and unable to provide adequate compensation. This breakdown leads to further thrombin generation and contributes to fibrin formation. Antithrombin levels also decrease in disseminated intravascular coagulation (DIC) due to several factors: 1) Continuous consumption of antithrombin due to ongoing coagulation; 2) Degradation of antithrombin and other proteins by elastase released from activated neutrophils as a result of protease inhibitor damage; 3) Loss of antithrombin due to capillary leakage; and 4) Impaired antithrombin production related to liver damage from reduced perfusion and microvascular coagulation. Low antithrombin levels in DIC correlate with increased mortality, particularly in septic patients. Decreased antithrombin levels often precede the onset of clinical manifestations of sepsis, indicating its involvement in the pathogenesis of DIC and its association with organ dysfunction.

Protein C system — Protein C plays a crucial role in anticoagulant compensatory mechanisms. Synthesized in the liver, protein C is activated to activated protein C (APC), which inhibits coagulation by inactivating factors V and VIII. Under normal conditions, protein C is activated by thrombin via thrombomodulin on the surface of endothelial cells. APC inhibits coagulation by proteolytically cleaving factors Va and VIIIa through binding to the endothelial protein C receptor (EPCR). Dysfunction of the protein C system in sepsis results from decreased thrombomodulin expression and inactivation by reactive oxygen species (ROS) on endothelial cells, mediated by pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-6. The observed depression of the protein C system in sepsis is attributed to excessive consumption, liver dysfunction, vascular leakage, and TNF-α activation.

Tissue Factor Pathway Inhibitor (TFPI) — Tissue factor pathway inhibitor (TFPI) is secreted by endothelial cells. TFPI reversibly inhibits factor Xa and irreversibly inhibits thrombin. It also possesses the ability to inhibit the TF-VIIa complex. Decreased TFPI levels are observed in sepsis. However, the precise role of TFPI in the pathophysiology of DIC remains incompletely understood. Experimental studies in humans have demonstrated that administration of recombinant TFPI can block thrombin generation induced by inflammation.

Disruption of the fibrinolytic system

In conditions of bacteremia and endotoxemia, an increase in fibrinolytic activity is observed, possibly due to the release of plasminogen activators by endothelial cells. This state is rapidly followed by the suppression of fibrinolytic activity by plasminogen activator inhibitor-1 (PAI-1). The persistently high levels of PAI-1 effectively halt fibrinolysis, leading to the accumulation of fibrin clots in the microcirculation.

A study found that patients with disseminated intravascular coagulation (DIC) and multiple organ failure exhibited elevated levels of tissue plasminogen activator (t-PA) antigen and PAI-1, accompanied by decreased levels of α2-antiplasmin compared to DIC patients without multiple organ failure. These findings support the conclusion that effective fibrinolysis is a crucial mechanism for preventing multiple organ failure.

Overall, DIC has two main consequences. First, it results in widespread fibrin deposition within the microcirculation. This leads to ischemia in the affected organs, making them more susceptible to damage, and causes hemolysis as erythrocytes are traumatized while passing through the fibrin meshwork (microangiopathic hemolytic anemia). Second, a bleeding diathesis occurs due to the excessive consumption of platelets and coagulation factors.

The situation is further exacerbated when extensive coagulation activates plasminogen. Plasmin not only breaks down fibrin (fibrinolysis) but also degrades factors V and VIII, further reducing their concentrations. Additionally, fibrinolysis results in the formation of fibrin degradation products (FDPs), which inhibit platelet aggregation, possess antithrombin activity, and impair fibrin polymerization. All of these factors can contribute to hemostatic failure.[3,9,10,14,15]

Diagnosis

Diagnosis of DIC relies on a combination of clinical manifestations and laboratory findings. However, no single laboratory test is sufficient to definitively diagnose or exclude DIC.[15] Recommended laboratory investigations aim to identify DIC, assess its severity, and monitor treatment efficacy over time. A single test is insufficient; rather, a combination of tests performed periodically is necessary to monitor patient improvement or deterioration. Recommended tests include D-dimer assay, fibrinogen blood test, prothrombin time (PT), fibrin degradation products (FDP), complete blood count (CBC), and partial thromboplastin time (PTT).[4]

In DIC, these ancillary tests may reveal prolonged PT and PTT, the presence of fibrin degradation products in plasma, decreased levels of coagulation inhibitors such as antithrombin, and a platelet count below 100,000 or a further decrease upon repeated testing. Although decreased platelet count is a sensitive indicator, it is not specific for DIC. The combination of a decreased platelet count and the presence of fibrin degradation products strongly suggests DIC.

Franchini et al.[16] in their journal article on the pathophysiology, diagnosis, and management of DIC, proposed a five-step algorithm for diagnosing DIC (Figure 3). The first step involves assessing the risk of DIC by identifying any underlying conditions that may predispose an individual to DIC. The second step, if risk factors are present, involves performing coagulation tests such as platelet count, PT, fibrinogen, and FDP. The third step analyzes the coagulation test results. The fourth step involves calculating a score using a scoring system, and the fifth step sums the obtained scores. A final score of ≥5 suggests a diagnosis of overt DIC, while a score of ≤5 suggests non-overt DIC.

Signs and symptoms of DIC depend on the underlying cause; however, general clinical manifestations of DIC include petechiae, hematuria, hypotension, spontaneous ecchymoses, respiratory tract bleeding, mucosal bleeding from the gums, mouth, and nose, bleeding from infusion sites, thrombosis, and bleeding from surgical wounds such as gastrointestinal bleeding and hematuria.

Several published literatures outline three guidelines for DIC from the British Committee for Standards in Haematology (BCSH), the Japanese Society of Thrombosis and Hemostasis (JSTH), and the Italian Society for Thrombosis and Hemostasis (SISET). While generally similar, these guidelines differ in their recommendations. Consequently, efforts were made by active members of the DIC subcommittee of the International Society of Thrombosis and Haemostasis (ISTH) to harmonize these three guidelines based on the Scientific and Standardization Committee (SSC).

According to the ISTH-recommended DIC guideline, there is no gold standard test for diagnosing DIC, nor is there a single laboratory test that can accurately diagnose DIC. The ISTH recommends using a scoring system to assess diagnostic quality. The following are the ISTH recommendations for diagnosing DIC: a) The use of a scoring system is strongly recommended for diagnosing DIC (Moderate Quality, Grade C, Level IV); b) The scoring system for DIC diagnostic criteria is known to strongly correlate with clinical monitoring and outcomes (Moderate Quality, Grade C, Level IV); and c) Repeated testing is crucial for monitoring dynamic changes based on laboratory results and clinical observations (Moderate Quality, Grade B, Level III).

Several scoring systems aid in diagnosing disseminated intravascular coagulation (DIC), developed by organizations such as the International Society on Thrombosis and Hemostasis (ISTH), the Japanese Ministry of Health, Labour and Welfare (JMHLW), and the Japanese Association of Acute Medicine (JAAM).

The ISTH scoring system for overt DIC is useful in diagnosing DIC resulting from both infectious and non-infectious causes. Conversely, the JAAM scoring system is particularly sensitive for detecting septic DIC. Some reports suggest that bleeding-type DIC is more readily diagnosed using the ISTH overt DIC criteria and the JMHLW criteria. For organ damage-type DIC, the JAAM criteria are more highly recommended.[17]

The second step in the overt DIC diagnostic algorithm involves performing global coagulation tests. These tests comprise a complete blood count (CBC), prothrombin time (PT), fibrinogen level, and fibrin degradation products (FDP) assay. The third step entails evaluating the results of these tests. From the CBC, the platelet count is assessed; a count >100 receives a score of 0, a count <100 receives a score of 1, and a count less than 50 receives a score of 2.[17]

These scores are then summed. A total score ≥5 indicates the presence of overt DIC, and daily repetition of this scoring system is recommended. However, a score <5 suggests non-overt DIC, and repeat testing within 1–2 days is advised.[17] In a survey of experts regarding DIC diagnosis, when choosing a scoring system for overt DIC, the majority (62%) opted for the ISTH overt DIC criteria, 3 experts (9%) preferred the JAAM score, 1 expert used the JMHLW criteria, 7 experts (20%) preferred a combination of blood tests without adhering to any of the three criteria, and 2 other experts did not use specific scores but rather based their assessment on the underlying cause, although the rationale for this approach remains unclear. Regarding non-overt DIC, 18 of 23 experts chose the ISTH criteria, 1 expert used JAAM, none chose the JMHLW scoring system, and the remainder opted for a combination of various supporting examinations.[18]

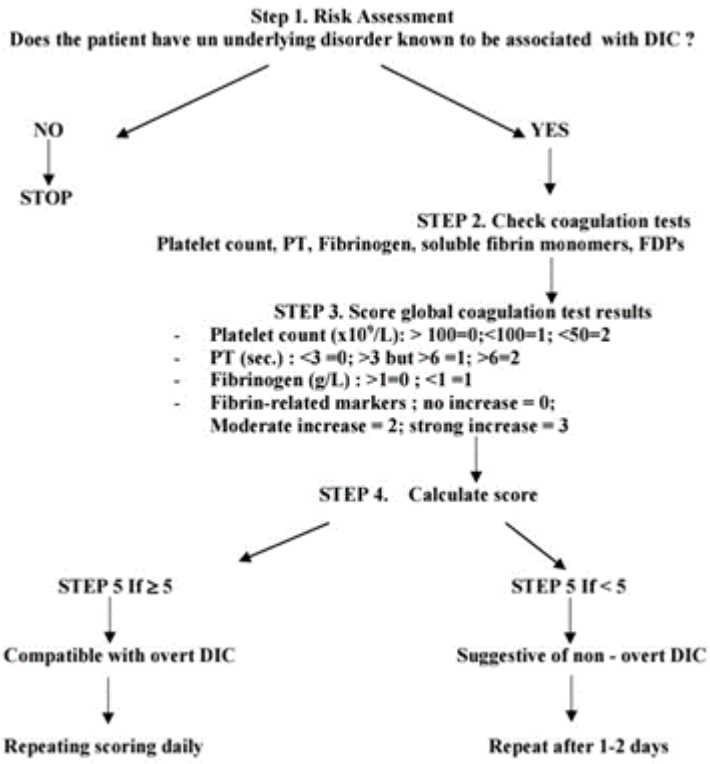

Figure 3. Five-step diagnostic algorithm for Disseminated Intravascular Coagulation (DIC).[16]

DIC therapy

In the European Union and the United States, the 2012 guidelines from the Surviving Sepsis Campaign do not recommend specific treatment for septic DIC. Conversely, in Japan, aggressive treatment of septic DIC is advocated; however, this does not necessarily imply that Japan is one of the most effective countries in treating patients with septic DIC.[11,19]

In the management of DIC, the primary therapy is addressing the underlying etiology. Without treating the primary disease causing DIC, therapies targeting the complications of DIC will be unsuccessful. Therefore, it is crucial to identify the underlying disease responsible for DIC. This may include administering antibiotics or performing drainage procedures in patients with infectious diseases, and administering anticancer drugs in patients with malignancies.[19] Nevertheless, treating the complications of DIC itself is imperative, such as acidosis, hypotension, hypothermia, and hypocalcemia. The therapeutic modalities will naturally vary depending on the specific complications that manifest.[4]

The fundamental principles of disseminated intravascular coagulation (DIC) management include: (1) supportive therapy, encompassing resuscitation, hemodynamic stabilization, vital sign monitoring, airway management, and correction of blood glucose, acid-base, and electrolyte imbalances; (2) treatment of the primary disease/infection control; and (3) inhibition of the pathological processes underlying DIC. The administration of platelet and coagulation factor transfusions aims not only to correct laboratory values but, more importantly, to mitigate the risk of bleeding based on clinical condition. Several DIC management guidelines recommend the administration of platelet concentrates (PC) and fresh frozen plasma (FFP) in DIC patients with active bleeding or those at high risk of bleeding during invasive procedures.[19] Platelet products are used to treat thrombocytopenia, while FFP is used to correct prothrombin time (PT) and partial thromboplastin time (PTT) prolongation. The threshold for PC administration depends on the

patient's clinical status; however, in general, PC is administered in DIC patients with massive bleeding and a platelet count <50 x 10^9/L. In patients undergoing chemotherapy, however, PC may be administered in the absence of bleeding and with a platelet count between 10-20 x 10^9/L. Nevertheless, PC and FFP transfusions are typically reserved for patients with massive bleeding or the bleeding type of DIC.[19]

In cases of disseminated intravascular coagulation (DIC) complicated by active bleeding, a platelet count between 20 x 10^9/L until 50 x 10^9/L represents a threshold at which platelet transfusion should be promptly administered at a dosage of 1–2 units/kg/day.[9,10,15] Heparin therapy can be considered as a therapeutic option for DIC due to its ability to enhance antithrombin III (AT-III) activity by binding to AT-III, thereby inactivating thrombin and other proteases, including coagulation factor Xa (FXa). Heparin is recommended for asymptomatic DIC patients to prevent the onset of venous thromboembolism (VTE). However, heparin use is strongly contraindicated in DIC patients with massive bleeding[20] as illustrated in Table 1 below.

Table 1. Replacement therapy for symptomatic DIC patients[10]

Replacement Therapy	Suggested Dosage	Clinical Indicators for Use
Fresh-Frozen Plasma	15-20 ml/kg	Symptomatic bleeding with fibrinogen < 100 mg/dL
Fibrinogen concentrates	2-3 g	Symptomatic bleeding with fibrinogen < 100 mg/dL
Cryoprecipitate	1 U / 10 kg	Symptomatic bleeding with fibrinogen < 80- 100 mg/dL
Platelet concentrates	1-2 U / 10 kg	Platelet count < 20.000 OR Platelet count < 50.000 with b

Patients with disseminated intravascular coagulation (DIC) are at high risk of venous thromboembolism (VTE); therefore, low molecular weight heparin (LMWH) has become the standard of care. Research by Liu et al. (2014) indicates that LMWH is superior to unfractionated heparin (UFH) in treating DIC due to the higher level of inhibition achieved by LMWH on coagulation factor Xa activation compared to thrombin. Given the high incidence of VTE in DIC patients, prophylaxis using UFH, LMWH, or mechanical methods has become standard practice in DIC management. The recommended UFH dosage for pre-DIC cases is 70 IU/kg body weight per hour via continuous infusion for 5–7 days.[4,20]

In addition to blood components and heparin, anti-Xa agents such as fondaparinux and danaparoid sodium are also recommended for deep vein thrombosis (DVT) prophylaxis after orthopedic surgery. However, the benefits of anti-Xa agents in other types of DIC or in critically ill patients are less well established.[13,21]

Antifibrinolytics are also considered effective for treating bleeding. However, antifibrinolytic treatment in patients with organ failure and asymptomatic DIC is not recommended.[3,5,17,19] Tranexamic acid is the preferred option for controlling excessive thrombolysis that exacerbates bleeding. Vitamin K can also be administered to treat vitamin K deficiency.[4] Prothrombin complex concentrate (PCC) administration offers advantages due to the small volume required, making it more beneficial for patients with fluid overload. However, a disadvantage is that PCC is deficient in a crucial coagulation factor, factor V, while DIC is characterized by a global deficiency of coagulation factors.[15,16]

Thrombomodulin can bind to thrombin and activate protein C. It also has benefits for inflammatory processes through its binding to high-mobility group B proteins. Wada et al. reported the results of a pharmacological study of plasma thrombomodulin administration in DIC patients. The study found that thrombomodulin administration at doses of 0.3–30 U/ml significantly inhibited thrombin generation and stimulated APC production. The study concluded that thrombomodulin could be considered a therapeutic option warranting further research.[10,11]

There is no single specific treatment for DIC. The goal of treatment is to promptly assess and treat the underlying cause. Identifying the underlying cause can limit excessive thrombin production, stabilize the patient's condition, and improve the likelihood of successful DIC therapy. Supportive therapy is necessary to inhibit the pathological processes of DIC, including correction of coagulation factors by replacing coagulants and fibrinogen with fresh frozen plasma (FFP) infusion, heparin to prevent blood clotting, cryoprecipitate, and platelet transfusion if the platelet count is low.

Prognosis

The prognosis of DIC is determined by the underlying cause and its severity. DIC scoring systems appear to be the most effective method for predicting DIC prognosis. Levi et al.[21] suggested in their publication that combining DIC scores with the Acute Physiology and Chronic Health Evaluation II (APACHE II) score for predicting prognosis in critically ill patients yields better predictive accuracy compared to using the APACHE II score alone for mortality prediction.

The use of the International Society on Thrombosis and Haemostasis (ISTH) overt DIC scoring algorithm can also predict mortality in DIC patients. Several studies have demonstrated that septic patients with DIC, as assessed by this scoring system, exhibit significantly higher mortality rates compared to septic patients without DIC.[4,20,21]

Conclusion

Sepsis is a major challenge and a leading cause of mortality in intensive care units among critically ill patients. Its prognosis is frequently worsened by complications, such as hemostatic disorders, including thrombocytopenia, coagulation abnormalities, and more complex conditions like DIC. DIC is a clinicopathological syndrome complicating various diseases, characterized by systemic blood coagulation activation and intravascular fibrin production. This can lead to thrombosis in small- and medium-sized blood vessels, potentially causing multiple organ dysfunction concurrent with platelet and coagulation factor consumption, resulting in clinical bleeding manifestations.

The clinical manifestations of DIC in sepsis are not primarily caused by the invading pathogen but rather by sepsis-induced complications, such as hypotension, coagulopathy, and multiple organ dysfunction, culminating in dysregulation of host inflammatory mediators. DIC is classified into two types: acute and chronic. Acute DIC develops when a large amount of procoagulants (tissue factor) enters the circulation within a short period (hours to days), for example, in endotoxemia, extensive tissue trauma, pregnant women with pre-eclampsia complications, or placental abruption. In contrast, chronic DIC typically develops slowly over weeks to months, with predominantly thrombotic clinical manifestations, often occurring in cancer, aortic aneurysms, and chronic inflammatory diseases.

Pathogenetically, sepsis is closely associated with the causative agent and the resulting inflammatory response, promoting fibrin formation and deposition through simultaneous and continuous mechanisms. Therefore, early detection of DIC in sepsis patients is crucial to prevent complications and disease progression.

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