

## Tackling a deadly global phenomenon: sepsis induced coagulopathy: A narrative review

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### Abstract

Sepsis is a potentially fatal illness marked by organ failure and the two main causes of which are shock and disseminated intravascular coagulation. Multi-organ dysfunction in sepsis is mediated by the inflammatory cytokine storm, while sepsis induced coagulopathy is mediated and accelerated by activation of pro-coagulative mechanisms. Regardless of the severity of sepsis, disseminated intravascular coagulation is a potent predictor of mortality in septic patients. Additionally, oxidative stress in sepsis causes renal ischaemia and eventually acute kidney injury. The first and foremost goal is to initiate resuscitation immediately, with treatment mainly focussing on maintaining a balance of coagulants and anticoagulants. A simpler and more universal diagnostic criteria is likely to improve studies on the spectrum associated with sepsis.

**Keywords:** Sepsis induced coagulopathy, Anticoagulants, Coagulants, DIC.

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### Introduction

Sepsis refers to life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis ensues with an infection in the body eliciting a systemic inflammatory response via the replication of the microorganism and/or via chemicals released by the pathogen, such as endotoxins, exotoxins and lipoarabinomannan (LAM), to name a few. In fact, in 2016, the Society of Critical Care Medicine and the European Society of Intensive Care Medicine redefined sepsis as a "life-threatening organ dysfunction".<sup>1</sup> The scientific standardisation subcommittee of the International Society on Thrombosis and Haemostasis has provided a definition of disseminated intravascular coagulation (DIC) as a

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syndrome that is acquired, characterised by the activation of coagulation within blood vessels leading to a loss of localisation, and caused by various factors that can harm the small blood vessels and result in organ dysfunction if the damage is severe enough. In addition, overt DIC is a term used to describe the advanced stage of DIC, in which the abnormal activation of the coagulation system and subsequent clotting and bleeding is widespread and clinically evident.<sup>2</sup> In overt DIC, the clotting factors and platelets are depleted, leading to excessive bleeding, while at the same time, microvascular thrombosis can cause organ damage and dysfunction.<sup>3</sup>

The inflammatory process commonly manifests into organ dysfunction in multiple major organ systems, leading to acute respiratory distress syndrome (ARDS), myocardial depression, hepatic dysfunction, acute kidney injury (AKI), mucosal bleeding in the gastrointestinal tract (GIT), DIC, as well as sepsis-associated encephalopathy in the central nervous system (CNS).<sup>4</sup> Shock and DIC are the major causes of organ dysfunction in sepsis.<sup>5</sup>

It is one of the major healthcare problems because of its association with high mortality rates, especially in low- and middle-income countries (LMICs) having limited healthcare facilities.<sup>6</sup> The latest statistics about the global incidence and mortality of sepsis are 48.9 million and 11 million, respectively. Studies around the world revealed that 29.5% of intensive care unit (ICU) cases have sepsis.<sup>6</sup> However, there is scarce data from LMICs, including Pakistan. An Asian study had 28.3% of the cases in ICU with a diagnosis of sepsis.<sup>7</sup> Moreover, a study in Pakistan identified sepsis in 8,759 of 31,111 patients, of whom 38.75% had severe sepsis and 9.97% required admission to ICU for further management. Mortality amounted to 9.8% for sepsis and 22.8% for severe sepsis.<sup>8</sup> In another study, the mortality was 39.74%.<sup>9</sup> A meta-analysis conducted on two randomised controlled trials (RCTs) performed in sub-Saharan Africa concluded a higher mortality index in comparison to countries that followed standard protocols.<sup>10</sup> A study reported more than 750,000 cases of severe sepsis per annum in the United States, and 27% of all ICU admissions being related to sepsis in the United Kingdom.<sup>11</sup> A study conducted reported that 70% of deaths related to chest infection were associated with sepsis, which further

strengthens the need for caution against sepsis in healthcare settings.<sup>12,13</sup>

Sepsis-induced coagulopathy (SIC) is distinctively characterised by endothelial dysfunction, along with derangement of the physiological coagulative and fibrinolytic mechanisms.<sup>14</sup> DIC is a powerful prognostic indicator of death in septic individuals, regardless of the severity of sepsis, where individuals with coagulopathy have poorer consequences compared to those who do not have it.<sup>15</sup> Despite the grave consequences of DIC in sepsis, less importance is given to the management of it in critically ill patients.<sup>16</sup> While criterion for DIC diagnosis is in practice, diagnostics for sepsis-associated coagulopathy remain unknown. Studies have suggested that the criteria should encompass features that are convenient to use in clinical practice, should be accurate, and should have prognostic indicators. Thus, to combat the mortal sequelae of sepsis-associated coagulopathy, a set criterion will help highlight individuals for whom immediate anticoagulation will prove beneficial.

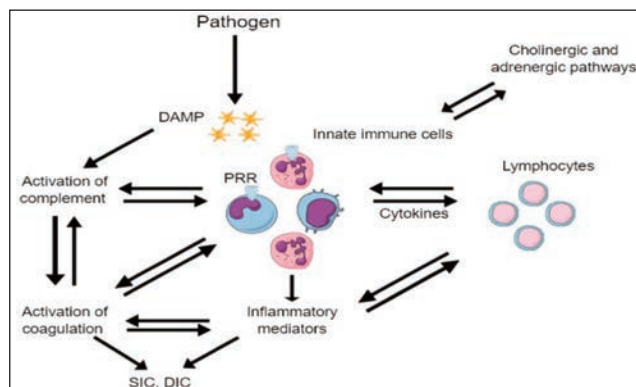
The current narrative review was planned to broadly address some key aspects of SIC, its pathophysiology, diagnostic parameters, treatment advances, treatment gaps, and the adoption of global clinical guidelines.

## Methods and Results

Peer-reviewed studies in the English language regardless of the study design published from 2001 to March 2023 were searched on PubMed, Embase and Cochrane databases.

### Pathophysiology of SIC

Activation of pro-coagulative mechanisms coupled with down-regulation of the normal anticoagulant mechanisms mediates and accelerates the pathophysiology of SIC. The tissue factor is present in monocytes and macrophages. The sepsis-induced inflammatory cytokine storm triggers the excessive release of tissue factor, which, by activating factor VII to VIIa, activates prothrombin to thrombin, which, thereafter, causes the conversion of soluble fibrinogen to insoluble fibrin while simultaneously activating coagulant factors, like VIII, IX and X. Meanwhile, tissue factor pathway inhibitor (TFPI), normally present in low concentration in the plasma, is consumed rapidly in sepsis,<sup>17</sup> leading to disinhibition of the extrinsic coagulation pathway and consequently a pro-coagulative state. The down-regulation of activated protein C (APC) precipitates a hypercoagulable state early in sepsis, while the down-regulation of endothelial protein C receptor (EPCR) in severe sepsis means that protein C cannot be activated.<sup>18</sup> Moreover, in addition to impaired synthesis, the rapid consumption and degradation of protein C by neutrophil elastase further



**Figure:** The pathophysiology of sepsis-induced coagulopathy (SIC). After a pathogen invades, antigens are recognised by pattern-recognition receptors (PRRs) in innate immune cells. These cells are then activated and release cytokines and inflammatory mediators. This leads to the activation of lymphocytes and the coagulation cascade, which ultimately leads to SIC and disseminated intravascular coagulopathy (DIC). Additionally, complement is activated by damage-associated molecular patterns (DAMPs), which also activates the coagulation cascade.<sup>2</sup>

lowers its plasma concentration.<sup>19</sup> Likewise, thrombin formation induces the synthesis of thrombin-activable fibrinolysis inhibitor (TAFI).<sup>20</sup> Moreover, endothelial cells normally synthesise tissue-type plasminogen activator (PA) and plasminogen activator inhibitor-1 (PAI-1), the cumulative effect of which again favours a pro-coagulative state in sepsis, stabilising the clot and making it resistant to fibrinolysis.<sup>21</sup> In severe sepsis, thrombin formation combined with the reduction in cytokine mediated heparin-like glycosaminoglycans on the endothelial surface together decrease anti-thrombin synthesis while simultaneously increasing its consumption remarkably, thereby contributing to the hypercoagulability.<sup>21,22</sup>

Recent advances in this field have unravelled further mechanisms possibly promoting coagulopathy in sepsis.<sup>23</sup> Both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) from pathogens may possibly stimulate monocytes to release cytokines and extracellular vesicles expressing pro-coagulant tissue factor and phosphatidylserine (Figure).

The cytokines and chemokines released will then promote coagulation by activating neutrophils, platelets, and endothelial cells. Meanwhile, the disruption of the glycocalyx causes endothelial cells to become pro-coagulative while expressing ultra-large von Willebrand factor (vWF). Likewise, neutrophils not only express tissue factor and stimulate the extrinsic coagulation pathway, but are also thought to release neutrophil extracellular traps (NETs), which comprise pro-coagulative deoxyribonucleic acid (DNA), histones and other DAMPs.<sup>24</sup>

### SIC complications

The inflammatory cytokine storm in sepsis is documented to mediate multi-organ dysfunction involving the cardiovascular, respiratory, renal, neurological, haematological and hepatic systems. While myocardial depression is the hallmark feature of the cardiovascular dysfunction induced by sepsis, respiratory dysfunction is depicted as hypoxaemia, leading to respiratory failure and fatigue along with tachypnoea.<sup>25</sup> Additionally, renal ischaemia resulting from the oxidative and nitrosative stress imposed by sepsis eventually leads to AKI.<sup>26</sup> This is commonly observed in critically ill patients and correlates significantly with mortality. The inflammatory cytokine release triggered by a bacterial infection decreases the availability of nitric oxide,<sup>27</sup> leading to mitochondrial damage and reduced cerebral perfusion, which, coupled with impaired membrane permeability and neuronal toxicity, leads to brain dysfunction in sepsis.<sup>28</sup> Likewise, cytokine-mediated apoptosis of hepatocytes commonly leads to dysregulated liver function in sepsis. Most importantly, DIC following coagulopathy constitutes one of the major causes of death in sepsis, and is mediated by several factors, including endothelial damage, the cytokine storm, NETs, histones, elastase and steps leading to activation of the coagulation cascade.<sup>29</sup>

Moreover, histone proteins released during NETosis are strongly suggested to play a role in cardiac dysfunction by enabling a cytotoxic effect on cardiac myocytes.<sup>30</sup> Hyper NETs' release is also associated with impairment of renal function in sepsis.<sup>31</sup> Meanwhile, NETs and histone proteins exhibit a cytotoxic effect on epithelial cells of the lung, where NETs are also correlated to reduced lung function.<sup>32</sup> Some research in mice has also demarcated the role of NETs in inducing haematological dysfunction in sepsis.<sup>33</sup>

### Outcomes: mortality and hospital stay

SIC stands as an independent predictor of in-hospital mortality in ICUs.<sup>33</sup> Additionally, it has been demonstrated that in the ICU setting, patients who develop sepsis during their stay have a significantly higher mortality risk and prolonged length of stay (LOS) compared to those without sepsis.<sup>34</sup> The severity of SIC is significantly linked to poor prognosis, meaning an increased inpatient LOS and mortality.<sup>35</sup> A meta-analysis of 51 studies demonstrated the risk of mortality to be significantly greater in ICU cases with hospital-acquired sepsis with organ dysfunction compared to the control group.<sup>36</sup> Moreover, an analysis of the epidemiology of severe sepsis (acute infection accompanied by organ dysfunction) in the United States divulged 28.6% mortality and an increasing trend of mortality with age, from 10% in children to 38.4% in those aged >85 years.<sup>11</sup> Meanwhile, a prolonged stay in the

emergency department (ED) is associated with a significant risk of mortality in patients suffering from severe sepsis.<sup>38</sup> While there is limited research conducted in this regard in Pakistan, the most recent analysis of a tertiary care hospital in Pakistan found that the mean LOS was much longer, with the risk of mortality also being 32 times higher in the severe sepsis group compared to the sepsis group. Patients with one or more organ dysfunctions were also at a 6-16 times greater risk of in-hospital mortality, with the greatest risk being in patients suffering from haematological, cardiovascular or respiratory dysfunction.<sup>8</sup> However, while some research has been done otherwise among patients with sepsis, the research done in the context of severe sepsis and SIC in Pakistan remains scanty, and, hence, no definitive conclusions can be made in this regard.<sup>38</sup>

### Treatment

The first and foremost goal of sepsis is to begin the resuscitation immediately. Surviving Sepsis Campaign (SSC) 2016 guidelines recommend fluid resuscitation of at least 30mL/kg of intravenous (IV) crystalloid fluid in the first 3 hours, and then reassessing the haemodynamic parameters to decide the next step.<sup>8</sup> SIC is a fatal consequence of sepsis that should be considered while treating for sepsis. The goal of SIC treatment is to maintain the balance between coagulants and anticoagulants.

### Heparin

The most routinely prescribed and widely accessible anticoagulants for a range of thromboembolic illnesses are unfractionated heparin and low-molecular-weight heparin (LMWH). Nevertheless, their efficacy in treating SIC or DIC is still controversial and is usually restricted to the prevention of deep vein thrombosis (DVT). A meta-analysis of 9 studies found that heparin treatment did not improve organ damage in most sepsis patients, but it did increase the risk of bleeding.<sup>39</sup>

### Antithrombin

Another regularly used anticoagulant, antithrombin, has demonstrated improved results in SIC treatment. A meta-analysis found that antithrombin had a positive effect on mortality in patients with sepsis and DIC.<sup>40</sup> The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock support the use of antithrombin for DIC patients with low antithrombin activity based on comparable findings from a meta-analysis in patients with sepsis-associated DIC.<sup>41</sup> In a network meta-analysis, Yatabe et al. examined the effects and adverse events of antithrombin, recombinant thrombomodulin, heparin, and synthetic protease inhibitors in 1,340 patients.<sup>42</sup> Although there were no significant differences in the risk of mortality or bleeding complications between the placebo and any

of the four anticoagulant therapy groups, taking antithrombin was linked with a 5-fold greater chance of DIC resolution compared to the placebo group.

### Combination therapy

Antithrombin is frequently used in conjunction with heparin because its anticoagulant action is considerably increased by its binding to heparin. However, according to a study, IV heparin appears to modify antithrombin's protective effect.<sup>43</sup> Together, it has also been proven to increase the risk of bleeding while decreasing mortality.<sup>45</sup> As a result, antithrombin should be given without concurrent heparin treatment.

### Recombinant activated protein C

Another major physiological anticoagulant process is the thrombomodulin-protein C system. Reduced production of protein C and its cofactor protein S, as well as decreased expression of thrombomodulin and EPCR on endothelial cells, resulting in decreased activation of protein C, which is essential for thrombin control. Activated protein C destroys coagulation factors Va and VIIIa via proteolysis, resulting in an antithrombogenic action. Recombinant activated protein C (drotrecogin) was produced, evaluated in a phase III study, and authorised as a new medication for sepsis based on the aforementioned rationale.<sup>45</sup> However, successive clinical trials failed to demonstrate a reduction in mortality and highlighted concerns regarding bleeding. As a result, the producer withdrew drotrecogin off the market.<sup>46</sup> Following that, a recombinant activated protein C variant with normal signalling via EPCR and proteinase-activated receptor 1 (PAR1), but minimal anticoagulant activity was created. Although a preclinical investigation demonstrated decreased mortality in an animal model of sepsis, the potential efficacy of this treatment method in humans has not been investigated.<sup>47</sup>

### Recombinant thrombomodulin

The effectiveness of recombinant human soluble thrombomodulin (ART-123) was demonstrated in phase III clinical trial. ART-123 therapy significantly improves DIC (66.1% in the ART-123 group vs. 49.9% in the heparin group) and alleviates bleeding symptoms in DIC patients when compared to heparin therapy (43.1% in the ART-123 group vs. 56.5 % in the Heparin group;  $p=0.0487$ ).<sup>48</sup> Following this investigation, a phase IIb trial was done, which revealed a 3.8% reduction in mortality rate that was not statistically significant.<sup>49</sup> Most recently, a multinational phase III study in 800 patients with sepsis, organ failure and coagulopathy (platelet count  $<150 \times 10^9/L$  and prothrombin time-international normalized ratio [PT-INR]  $>1.4$ ) found a 2.6% reduction in death, which was not statistically significant.<sup>50</sup> Yamakawa et al. observed a 13% reduction in

death rate in a meta-analysis of all ART-123 studies (relative risk [RR]: 0.87, 95% confidence interval [CI]: 0.74-1.03,  $p=0.10$ ).<sup>51</sup> ART-123, in contrast to activated protein C, is associated with a decreased risk of bleeding, possibly due to thrombomodulin's antifibrinolytic effect, and is less likely to induce bleeding. Furthermore, circulating levels of activated protein C activity did not rise following ART-123 treatment.<sup>52</sup> This supports the use of recombinant thrombomodulin to treat sepsis-related DIC or SIC.

### Recombinant tissue factor pathway inhibitor

Another significant anticoagulant system is the tissue factor pathway inhibitor (TFPI), which influences the coagulation system by directly attaching to the tissue factor-Factor VII/Factor VIIIa complex and Factor Xa. Because tissue factor is important in sepsis-associated DIC, inhibiting it is considered to be beneficial. Concerning the use of recombinant TAFI (tifacogin), an RCT failed to demonstrate any benefit to improve mortality rates.<sup>54</sup>

Because there is no known cure, clinicians frequently see DIC as an acronym for "Death Is Coming". Differences in the diagnosis and therapy of sepsis-associated DIC have hampered improvements in the understanding/management of this illness despite increased concerns about sepsis and prospective therapeutics to reduce mortality. It is felt that targetted therapy employing precision medicine, namely anticoagulants, is useful in sepsis, but will not be beneficial unless the patient also has DIC. Early detection of the coagulation issue and immediate beginning of targetted anticoagulant medication may improve sepsis outcomes, although early and rapid detection is critical for this therapeutic approach.

### Fresh frozen plasma (FFP)

FFP administration to sepsis patients can have positive or negative effects. In one study, FFPs were used to treat the sickest patients who were in septic shock and had an abdominal emphasis. There was no influence on mortality after propensity scores were considered. The effectiveness of shock reversal and the need for fluid and vasopressors were unaffected by plasma therapy.<sup>54</sup> Because there is little evidence of any risk-benefit ratio in the management of SIC, the current recommendations advise against utilising plasma in septic shock unless there is a clear rationale for doing so.

### Regional guidelines

As anticoagulation can help treat DIC, identifying affected patients is crucial for timely recognition. Practices followed in an LMIC like Pakistan include monitoring markers of sepsis, such as D-dimer, PT and activated partial thromboplastin time (aPTT) in high-risk patients for prompt



**Table:** International Society of Thrombosis and Homeostasis (ISTH) criteria for DIC and SIC diagnoses.

	Overt DIC by ISTH	Overt DIC by ISTH
<b>Platelet Count</b>	50,000 - 100,000/pl: 1 point <50,000/ $\mu$ L: 2 points	<100,000/ $\mu$ L: 1 point
<b>Prothrombin time (PT)/ activated partial thromboplastin time (aPTT)</b>	Prolongation of PT 3-6 sec: 1 point >6 sec: 2 points	Prolongation of PT >3 sec: 1 point or Prolongation of aPTT >5 sec: 1 point
<b>Fibrinogen</b>	<100 mg/dL: 1 point	<150 mg/dL: 1 point
<b>D-dimer</b>	0.5-1: 1 point 1-2: 2 points >2 (ug/mL): 3 points	Increase: 1 point
<b>Total</b>	Overt DIC $\geq$ 5 points	Overt DIC $\geq$ 3 points

DIC: Disseminated intravascular coagulation, SIC: Sepsis-induced coagulopathy, FDP: Fibrin degradation products.<sup>59</sup>

recognition and diagnosis of sepsis. However, various scoring criteria are in place for appropriate diagnosis of sepsis and SIC. The International Society on Thrombosis and Haemostasis (ISTH) developed an 8-point scoring system in 2001 using the following parameters: platelets, D-dimer, fibrin degradation products, PT and fibrinogen, where a score  $\geq$ 5 detected severe DIC versus a score  $\geq$ 4 detecting SIC.<sup>55</sup> D-dimer was seen to be the most predictive of sepsis and SIC. This scoring criterion has a good overall positive predictive value (PPV).<sup>56</sup> Moreover, in 2017, SIC scoring system diagnosed SIC using the functionality of respiratory, cardiovascular, hepatic and kidney functions, along with platelet number and INR. A score  $\geq$ 4 increased the risk for SIC.<sup>57</sup>

The ISTH has provided guidelines for diagnosing overt DIC, which emphasise laboratory parameters. The criteria now include D-dimers for the first time, while the importance of platelet count has been reduced and the significance of fibrin-related markers has been increased. According to these guidelines, elevated levels of fibrinogen-degradation product (FDP) or D-dimers, decreased platelet count, prolonged PT, and decreased fibrinogen levels indicate overt DIC (Table).<sup>58</sup> Other scoring systems, such as the Japanese Association for Acute Medicine (JAAM) DIC diagnostic criteria, also consider platelet count, FDP concentration, PT and systemic inflammatory response as important criteria for DIC diagnosis.<sup>60</sup>

Although the DIC score has proven to be a good predictor of mortality, it is typically identified at an advanced and irreversible stage of coagulopathy, which makes therapeutic intervention less effective.<sup>59</sup> To address this issue, the ISTH DIC subcommittee has recommended simple diagnostic criteria for SIC that can be used to identify patients earlier. The SIC criteria include three parameters: platelet count, PT or INR, and sequential organ failure assessment (SOFA) score, with the presence of sepsis confirmed by the updated sepsis definition reflected in the SOFA score.<sup>2</sup> Sepsis-associated DIC is characterised by

impaired fibrinolysis, which results from excessive production of PAI-1, leading to a prothrombotic state and organ dysfunction due to tissue hypoperfusion.<sup>2</sup> In contrast, non-sepsis DIC typically presents with systemic bleeding rather than suppressed fibrinolysis, and reduced fibrinogen levels are not a common or specific finding in sepsis, unlike thrombocytopenia and PT prolongation.<sup>2</sup> Notably, FDPs and D-dimers were not included in the SIC score due to their lack of correlation with sepsis severity. This means that the SIC score is twice sensitive compared to the overt DIC score. Notably, overt DIC is always followed by SIC.<sup>59</sup>

Besides, the most recent guidelines, i.e. SSC 2021, highly recommend using the well-known systemic inflammatory response syndrome (SIRS) criteria for appropriate screening of sepsis. Moreover, for venous thromboembolism (VTE) prophylaxis, LMWH is preferred over unfractionated heparin due to lower rates of DVT. In addition, its administration is more convenient in LMICs and at an individual level due to the subcutaneous route of administration daily. Where pharmacological prophylaxis for VTE cannot be done, mechanical prophylaxis can prove to be helpful.<sup>60</sup>

## Discussion

Coagulopathy is a significant and common complication of sepsis that causes organ failure. Sepsis is a leading cause of thrombocytopenia and vascular injury, and it can lead to DIC, also known as SIC. The decompensated condition of coagulopathy, which can also be induced by acute damage, cardiogenic shock, or multi-organ injury, is represented by DIC as laboratory-based diagnostic markers. Coagulopathy in sepsis is commonly misdiagnosed or misclassified, and DIC is classified into numerous types. The diagnosis of either SIC or overt DIC may help identify patients who could benefit from therapeutic anticoagulant intervention. To facilitate the timely identification of suitable candidates for anticoagulant treatment, the ISTH has developed a "two-step" sequential scoring system (Table). Patients are first screened using the SIC score, and if the criteria for SIC are met, the overt DIC score is then calculated. This approach increases the likelihood of timely identification of eligible patients for anticoagulant treatment.<sup>61</sup>

Other diseases that can develop in critically ill patients, such as thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome, can occur in sepsis patients and should be treated. Although SIC is diagnosed using a combination of haemostatic markers, new methods for easier detection may develop in the future. Continued efforts to develop innovative medicines for these

complicated diseases, as well as a more targeted approach, are necessary. A strategy to determine the particular consequences of DIC should be investigated in both laboratory and clinical studies. Coagulopathy in sepsis is a dynamic process with many manifestations, and there is currently a lack of effective instruments to assess this dynamic shift in sepsis. Furthermore, there is a lot of bias in the available research that has to be addressed, and high-quality clinical studies should be conducted to establish SIC treatment globally.

### Conclusion

DIC is a potentially fatal complication of septic patients characterised by systemic coagulation activation. In terms of therapeutic interventions, there are significant variances between countries. However, heparin does not play a significant role as anticoagulant. Antithrombin should be given without concurrent heparin treatment. Antithrombin and recombinant thrombomodulin are approved, although an effect on mortality has yet to be established. As far as FFP is concerned, current recommendations advise against utilising plasma in septic shock cases. However, because sepsis is the most common and deadly cause of DIC, and if monotherapy is insufficient, combination therapy should be considered. Simpler and uniform diagnostic criteria will improve research on the sepsis-associated SIC/DIC spectrum.

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**Author Contribution:**

AA: Identified the topic, writing, literature search, reviewing, editing of final draft.

WA: Writing and reviewing of final draft.

NR: Revision and added new data to it, editing of final draft.

ZN: Wrote treatment and gaps of first draft.

ZG: Reviewing, editing and wrote the final draft