Review

Coagulopathy and sepsis: Pathophysiology, clinical manifestations and treatment

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ABSTRACT

Sepsis is a complex syndrome with a high incidence, increasing by 8.7% annually over the last 20 years. Coagulopathy is a leading factor associated with mortality in patients with sepsis and range from slight thrombocytopenia to fatal disorders, such as disseminated intravascular coagulation (DIC). Platelet reactivity increases during sepsis but prospective trials of antiplatelet therapy during sepsis have been disappointing. Thrombocytopenia is a known predictor of worse prognosis during sepsis. The mechanisms underlying thrombocytopenia in sepsis have yet to be fully understood but likely involves decreased platelet production, platelet sequestration and increased consumption. DIC is an acquired thrombohemorrhagic syndrome, resulting in intravascular fibrin formation, microangiopathic thrombosis, and subsequent depletion of coagulation factors and platelets. DIC can be resolved with treatment of the underlying disorder, which is considered the cornerstone in the management of this syndrome. This review presents the current knowledge on the pathophysiology, diagnosis, and treatment of sepsis-associated coagulopathies.

1. Introduction

Sepsis was redefined in 2016, by the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), as life-threatening organ dysfunction caused by a dysregulated host response to infection [1].

Sepsis is a complex clinical syndrome, with high incidence, estimated to be approximately 2.5 per 1000 in the Western world, which has been increasing 8.7% annually over the last 20 years, in part due to ageing of the population, with up to 2.8 million deaths per year attributable to sepsis in high-income countries [2,3]. Most deaths due to sepsis happen however in low-resource countries, where the exact incidence of sepsis is difficult to accurately estimate [2].

Treatment of sepsis is focused on adequate antibiotic therapy, source control, and appropriate supportive care and organ function replacement, if required [3]. The activation of coagulation and inflammation are essential reactions for host defence during sepsis [4]. Microbial pathogen-associated molecular patterns are recognized by pattern-

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recognition receptors, including Toll-like receptors (TLRs), on the cells of the innate immune system, which triggers the release of both proinflammatory and anti-inflammatory mediators [5]. Cytokines, such as tumour necrosis factor (TNF) α, interleukin (IL) 1, 2, 6, 8, and others, cause neutrophil–endothelial cell adhesion, activate the complement and clotting cascades, and can lead to the generation of microthrombi (Fig. 1) [5].

Virtually all patients with sepsis have coagulation abnormalities [3]. Sepsis-associated coagulopathies range from subtle activation of coagulation that can only be detected by sensitive markers for coagulation factor activation to somewhat more stronger coagulation activation that may be detectable by a small decrease in platelet count and subclinical prolongation of global clotting times to fulminant disseminated intravascular coagulation (DIC), characterized by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites [6,7]. The coagulopathy of DIC is variable from bleeding diathesis to hypercoagulability manifestations, all due to similar underlying pathophysiologic responses.

This review presents the current knowledge on the pathophysiology, diagnosis, and treatment of sepsis-associated coagulopathies, focussing on the role of platelets and the coagulation cascade and therapies that modulate these. Though, for the purposes of organisation, these are considered separately, it should be emphasized that these processes typically occur simultaneously with complex crosstalk.

2. Pathophysiology of platelets and the coagulation cascade in sepsis

2.1. Pathophysiology of platelet activation in sepsis

Platelet reactivity increases during sepsis [8]. Platelets possess damage associated molecular pattern (DAMP) receptors such as TLR 4, which is activated by factors such as bacterial endotoxin [9]. Increased circulating levels of hormones such as epinephrine and 5-hydroxytryptamine during sepsis also increase platelet reactivity via specific receptors [10–12]. Emphasising interaction between cellular and acellular arms of coagulation, sepsis is also associated with increased thrombin generation by the coagulation cascade, which activates platelets via protease-associated receptors (PAR) 1 and 4 [13,14].

Upon platelet activation, several processes of direct relevance to sepsis occur. Dense and alpha granules fuse with the cell membrane [14]. Dense granules are rich in adenosine diphosphate, which further stimulates and amplifies platelet activation via receptors $P2Y_1$ and $P2Y_{12}$, whilst alpha granules contain P-selectin that mediates activation of leukocytes via binding to P-selectin GP ligand (PSGL)-1; chemokines; and pro-coagulant factors. Platelet aggregates, resulting in micro or macrothrombosis, are formed by activation of GPIIb/IIIa, bridged by fibrinogen or von Willebrand Factor (vWF). Levels of both fibrinogen and vWF synthesis/release are typically increased during sepsis, vWF also facilitating platelet adhesion to the endothelium [15]. Mechanical

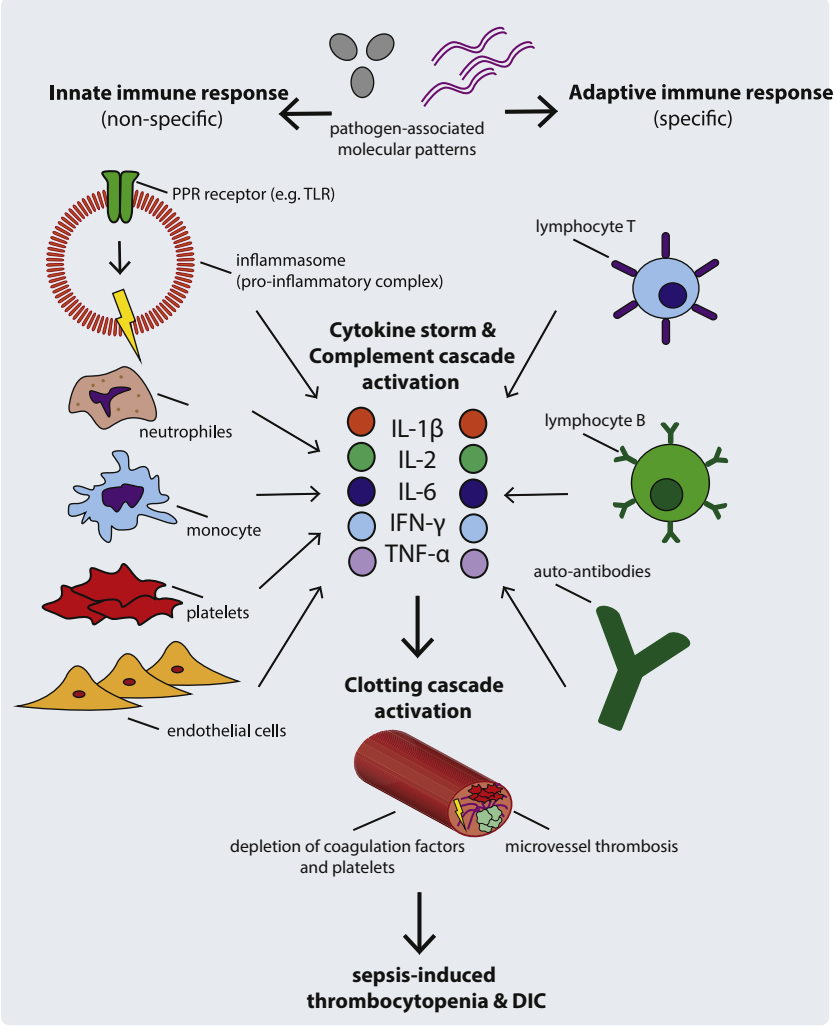

Fig. 1. Pathophysiology of coagulation disorders in sepsis.

interactions are potentiated by change from discoid to stellate shape [16]. Stimulation of platelet cyclo-oxygenase during platelet activation results in the generation of the inflammo-modulatory eicosanoids thromboxane A_2 and prostaglandin E_2 [17].

There is evidence that cytokines released during sepsis can directly activate platelets too, for example IL-6 can stimulate the collagen receptor glycoprotein (GP) VI [18]. Sepsis is also associated with increased release of platelets from the bone marrow leading to thrombocytosis, mediated by increased levels of thrombopoetin and potentiation by cytokines such as IL-6 [19]. Fig. 2 shows the role of platelets and coagulation cascade in patients with sepsis.

2.2. Pathophysiology of coagulation cascade activation in sepsis

Endothelial damage by bacterial toxins leads to upregulation of tissue factor, which activates factor VII, triggering the extrinsic pathway of the coagulation cascade [20] (Fig. 2). There is crosstalk with the intrinsic pathway via activation of factor VIIa by factor IX. As discussed above, thrombin generation also leads to platelet activation and conversely activated platelets contribute to thrombin generation via membrane and release of pro-coagulant factors upon degranulation. As well as an increase in procoagulant factors, hypofibrinolysis is mediated by thrombin-activatable fibrinolysis inhibitor (TAFI) [21].

These processes are associated with significant changes in fibrin clot dynamics, including a reduction in fibrin fibre diameter and increases in network density and clot turbidity and lysis area [22].

3. Specific clinical manifestations of sepsis-associated coagulopathy

3.1. Sepsis-related thrombocytopenia

3.1.1. Epidemiology

Thrombocytopenia is a common finding during sepsis and in particular during severe sepsis. Incidence of thrombocytopenia varies in different studies from 10% to up to 70% increasing in cohorts characterized by patients requiring intensive care unit (ICU)-treatment [23–25]. Usually defined as a platelet count <150.000/µl, thrombocytopenia is a known independent predictor of worse prognosis in sepsis patients [26–28]. Thus, a reduced platelet count has been included in widely used risk scoring systems such as the SOFA (Sequential Organ Failure Assessment) [29].

3.1.2. Causes

The mechanism behind thrombocytopenia in sepsis still needs to be completely understood but it probably derives from a combination of decreased platelet production, platelet sequestration and increased consumption [30–38].

Several causes have been proposed for thrombocytopenia in patients with sepsis and may often occur simultaneously. An increase of platelet sequestration is observed in the early phase of sepsis when platelets, after their activation, aggregate with leucocytes to form platelet-leucocyte aggregates (PLA) [33]. PLA can also cause thrombocytopenia through the release of platelets-activating neutrophil extracellular traps (NETs). In addition, infections can directly and indirectly cause thrombocytopenia by stimulating platelet activation and aggregation [34]. Bacteria such as *Staphylococcus aureus*, *Escherichia coli*, or Streptococcus Pneumonia directly stimulate platelet activation and PLA formation by binding and activating platelet receptors like TLRs or by involving plasma proteins such as complement proteins and fibrinogen [35]. Indirectly, the release of various antimicrobial peptides may lead to tissue damage and cell destruction causing inflammation and subsequently platelets activation and thrombocytopenia [32]. In pneumococcal infections, the clearance of platelets is increased by a process of platelet desialylation consisting of the release of neuraminidase and exposure of galactose residues [36]. During gram-positive and gram-negative infection, platelets may also be targeted by antibodies or reduced by disseminated intravascular coagulation (DIC) [37]. Finally, two other potential causes of thrombocytopenia in sepsis may be hemophagocytosis or altered platelet production [31]. Interestingly, the levels of newly produced and released platelets in peripheral blood, defined as immature platelet fraction (IPF), are higher in patients with severe sepsis and IPF correlates with sepsis severity scores [39]. This parameter has been suggested as a new biomarker to detect high-risk patients suffering from severe sepsis.

3.1.3. Differential diagnosis

While sepsis is one of the most common reasons for reduced platelet

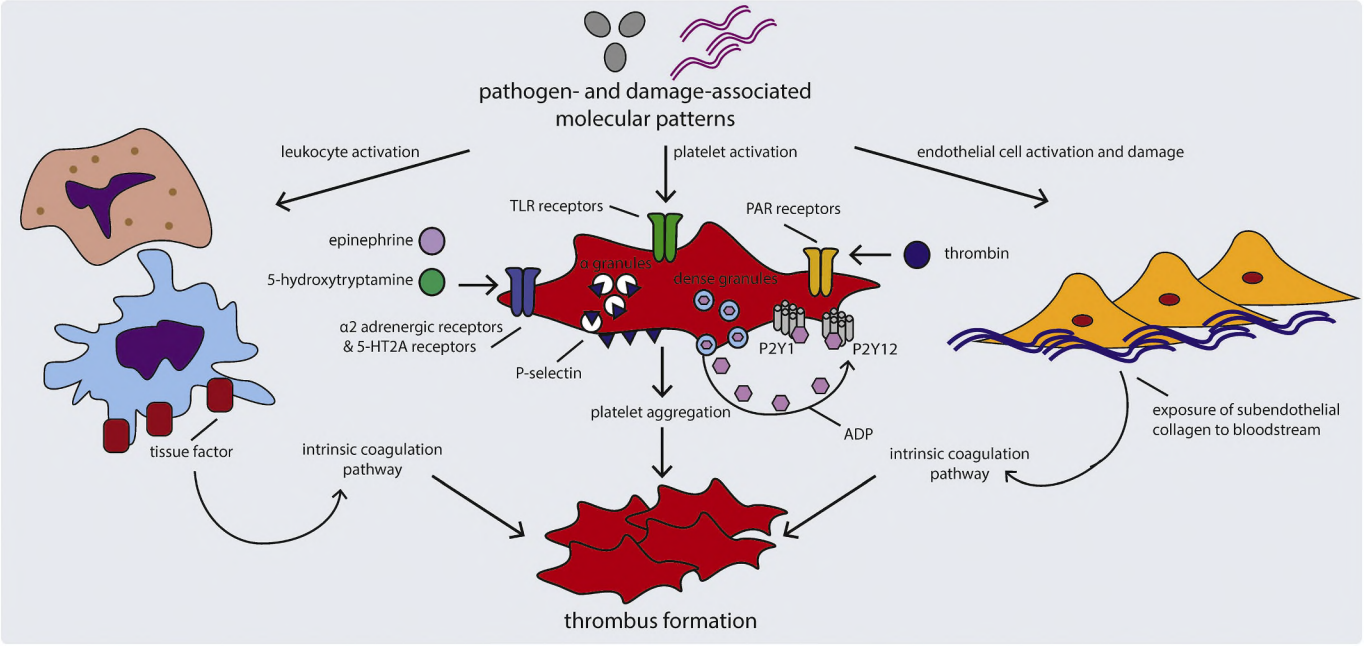

Fig. 2. The role of platelets and coagulation cascade in patients with sepsis.

count in critically ill patients, several other causes can mimic sepsis-related thrombocytopenia and represent a clinical challenge in patients requiring ICU treatment [27]. A systematic analysis of patients' clinical history (comorbidities, malignancy, exposition to heparin, etc.), as well as wide blood tests including, coombs antibodies and immature platelet fraction (to assess production), are important to thoroughly evaluate and rule out the most common differential diagnosis. Of note, overlapping mechanisms are not uncommon and complicate the clinical interpretation.

Possible differential diagnosis can be grouped into three categories: decreased production; increased destruction and platelet sequestration. Impaired platelet production could derive from myelodysplastic syndromes and aplastic anemia [40]. In addition, several drugs could also reduce platelet production such as chemotherapic agents and thiazides, which are known to directly suppress megakaryocyte platelet production.

However, thiazides can also induce severe thrombocytopenia due to an immune-mediated mechanism [41]. Common causes of platelet consumption and destruction are the disseminated intravascular coagulopathy (DIC) [42] and thrombotic microangiopathies as the hemolytic–uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) [43]. Furthermore, several drugs can induce platelet destruction and mimic sepsis-induced thrombocytopenia [44–46]. Immune-mediated platelet consumption is not limited to heparin-induced thrombocytopenia (HIT) and is associated with many other medicaments able to cause drug-induced immunologic thrombocytopenia by different mechanisms. Numerous drugs have been reported to induce drug-induced immunologic thrombocytopenia as cinchona alkaloid derivatives, penicillin, sulfonamides, nonsteroidal anti-inflammatory drugs, anticonvulsants, antirheumatic, oral antidiabetic drugs, diuretics, rifampicin, and ranitidine. For a structured review of the pathophysiological mechanisms leading to drug-induced thrombocytopenia, we refer to the work of Visentin and Liu [44]. At last, increased splenic sequestration occurs in patients with severe liver cirrhosis [47].

A diagnostic flow-chart of differential diagnosis of thrombocytopenia in patients with sepsis is shown in Fig. 3.

3.2. Disseminated intravascular coagulopathy

3.2.1. Definition

DIC is an acquired thrombohemorrhagic syndrome that is characterized by the dysfunctional systemic activation of coagulation pathways resulting in intravascular fibrin formation, microangiopathic thrombosis, and subsequent depletion of coagulation factors and platelets. This phenomenon is a host immune response to infectious insults such as sepsis, non-infectious causes such as trauma or it can be triggered by malignant disease [48,49]. It should be noted that trauma-induced DIC is marked by the distinct coagulopathic response primarily due to fibrinolytic phenotype and other contributing factors such as anemia, hemodilution, hypothermia, acidosis, and similar [50]. All these triggers can induce a damage to microvasculature thus precipitating vascular hypoperfusion of various organs and tissues with possible progression to necrosis and ultimately to multiorgan failure [48]. The key event is the loss of localized activation of the coagulation cascade at the site of injury to the blood vessel and subsequent inadequacy of natural inhibitors to check coagulation and blunt excessive thrombin generation [48].

In 2001, the Scientific Subcommittee on DIC of the International Society on Thrombosis and Hemostasis (ISTH) proposed a nomenclature in which DIC is recognized as a) non-overt and b) overt, as determined by specified clinical and hemostatic laboratory criteria [51]. In its non-overt form, DIC is conceptualized as the state of stressed but still compensated homeostatic system that is in the early phase of its evolution while overt DIC is considered as a decompensated homeostatic state in which physiological derangements are at the advanced severity

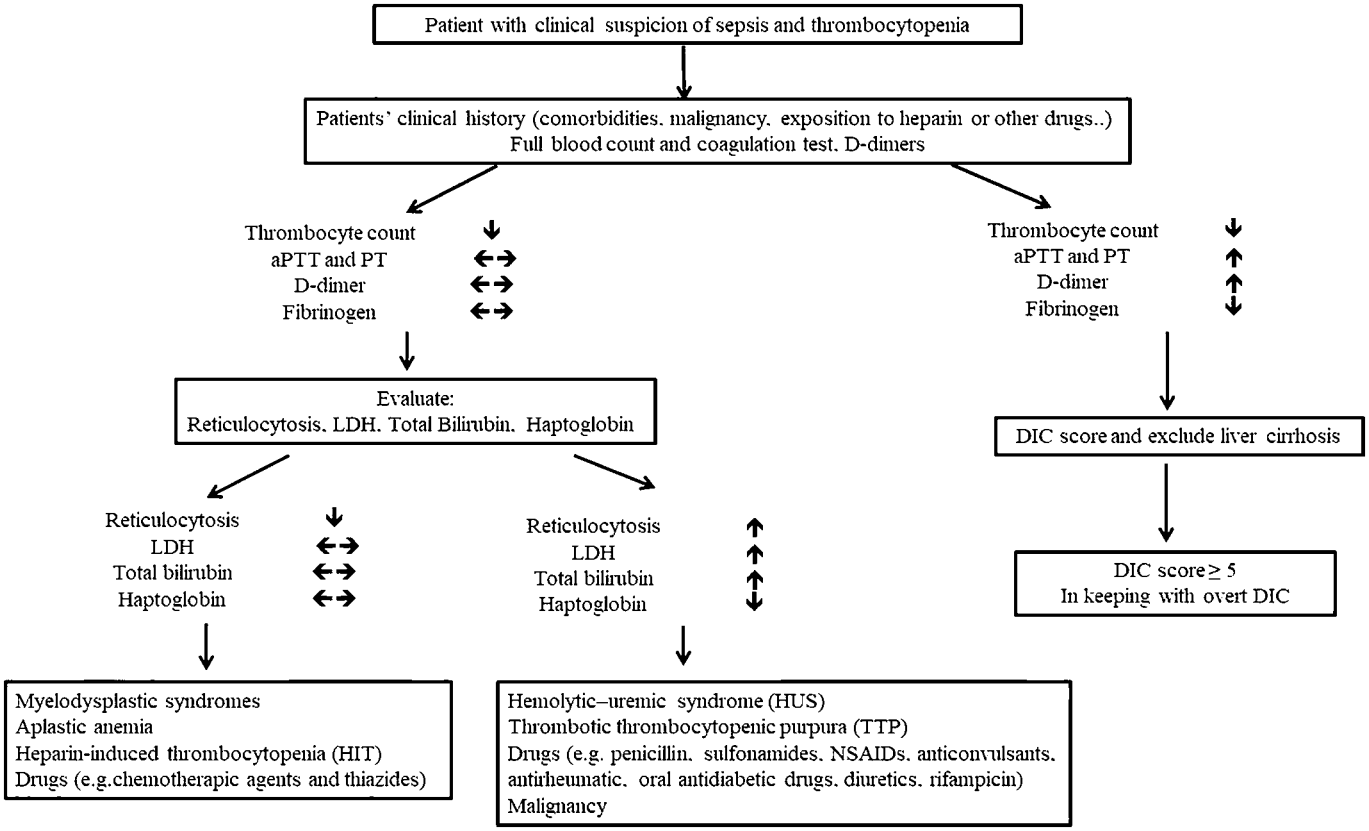

Fig. 3. Flow-chart of differential diagnosis of thrombocytopenia in patients with sepsis.

point and the full clinical syndrome of the DIC is evident. In more recent times, Papageorgiou and colleagues defined DIC as a clinicobiological syndrome marked by systemically dispersed and uncontrolled activation of coagulation that is associated with macro- and microvascular thrombosis and progressive consumption coagulopathy which may lead to an exuberant bleeding risk [52]. For the didactic purposes, it might also be useful to differentiate acute vs. chronic DIC in which acute form is characterized by the abrupt and sudden release of large amounts of tissue factor into the intravascular space thus creating generalized microvascular obstruction, rapid consumption of platelets and coagulation factors and multiorgan failure [53]. On the other hand, chronic DIC occurs in the scenario in which there is less intense but more persistent thrombin generation over a longer period of time such as e.g. in cancer or in the presence of retroperitoneal hematoma [54].

3.2.2. *Pathophysiology*

The pathophysiology of DIC is complex and includes at least a few known mechanisms that occur at the same time and/or sequentially. Briefly, the cardinal underlying disease process (such as mechanical endothelial injury in trauma, sepsis-induced inflammation, obstetric complications or cancer) triggers tissue factor (TF) over-release that leads to an excessive generation of thrombin, a central serine protease that converts soluble fibrinogen into insoluble fibrin strands and also stimulates higher production of itself by activating other coagulant enzymes and factors such as factor VIII, IX, and XI. Due to the principal insult and potent agonism by thrombin, platelets become activated and start to aggregate as a key part of the primary hemostatic mechanism and subsequently they stimulate secondary hemostasis (coagulation system) through the TF/factor VIIa axis and upregulate inflammation pathways through a mechanism involving factor XIIa/kallikrein/bradykinin/C3a [53,55]. Moreover, platelets regulate the coagulation cascade by stimulating thrombin generation through multiple cellular pathways [55]. Complement-mediated reactions serve a function to lyse cells and/or bacterial pathogens that upon destruction release damage-associated molecular patterns (DAMPs) and/or pathogen-associated molecular patterns (PAMPs) and other cellular components that can promote coagulopathy.

As fibrinous clot starts to form, the fibrinolytic cascade activates to counteract increasing fibrin deposition and aggregation in the microvasculature, however, this fibrinolytic activity may be significantly impaired by antifibrinolytic elements such as plasminogen activator inhibitor (PAI-1), thrombin-activatable fibrinolysis inhibitor (TAFI) and other prothrombotic mediators [56,57]. Similarly, physiological anticoagulant pathways consisting of tissue factor pathway inhibitor (TFPI), antithrombin (AT), and activated protein C (APC) are impaired in their activity and are thus are unable to sufficiently suppress the progressive procoagulant state. The present coagulation abnormalities are in bidirectional crosstalk with inflammatory mediators thus inflammation is a potent inductor of the coagulation cascade while coagulopathy significantly modifies and sustains inflammatory activity [58,59]. Proinflammatory cytokines such as IL-1, IL-6, TNF-α, elastase, and cathepsin G are important components of the humoral response to sepsis [60]. Recent advances in the field have elucidated the role of other factors contributing to the thromboinflammatory response such as NETs, extracellular vesicles, and endothelial glycocalyx shedding [61]. Taken together, it could be stated that DIC is the end-product of the pathophysiological ‘perfect storm’ in sepsis as it involves endothelial dysfunction and intravascular injury, potent initiation of coagulation pathways and platelet aggregation, impairment of anticoagulant systems, fibrinolytic shutdown, activation of the complement system, and upregulated inflammatory response thus creating a vicious circle and inflicting deleterious injuries on multiple organ systems, predisposing patients to poor outcomes (Fig. 1).

3.2.3. *Diagnosis*

Until recently, the approach towards diagnosis of DIC was heterogeneous since no single biomarker or clinical variable is sufficiently sensitive or specific in isolation thus it was difficult to establish uniform diagnostic criteria for DIC. The DIC is the pathologic diagnosis and the fundamental question asked is whether a patient has an underlying condition that might precipitate DIC accompanied with the clinical evaluation of typical manifestations such as bleeding, skin changes, or evident signs of organ dysfunction due to microvascular thrombotic obstruction. Although many different underlying causes could induce DIC, there are different pathogenetic mechanisms that perpetuate coagulopathy in different clinical scenarios [62]. For example, in a septic patient, tissue hypoperfusion is a crucial element that precipitates septic organ failure while shock and DIC are two notable complications that poorly impact patient outcomes [63]. It has been demonstrated that about one-third of patients with sepsis admitted to ICU will develop shock and in those with shock more than half will develop DIC [64]. Likewise, sepsis-induced DIC will dominantly be marked with organ dysfunction, excessive suppression of fibrinolysis, activated coagulation, and blunted anticoagulant system while hematologic malignancy-induced DIC will more likely be manifested with bleeding complications.

As previously mentioned, the ISTH published diagnostic criteria for overt DIC based on laboratory tests reflecting thrombosis and hemostasis, including platelet count, fibrin degradation products (FDP)/D-dimer, prothrombin time (PT), and fibrinogen [51]. It was later shown that overt DIC diagnosed by the ISTH-proposed score correlated with disease severity in hospitalized patients, however, it proved less useful in determining when to initiate anticoagulation treatment [65,66]. Since sepsis is a condition in which it is of paramount importance to minimize delays in diagnosis and intervention, it was soon proposed that both assessments of coagulation status and organ dysfunction must be integrated in order to identify ‘sepsis-induced coagulopathy (SIC)’ among sepsis patients in whom DIC is suspected [67]. Organ dysfunction is evaluated through SOFA score that was based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) published in 2016 [1]. The SOFA score takes into account respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems, and score ≥ 2 was associated with an in-hospital mortality greater than 10% [1]. The newly established SIC score is generated based on the platelet count, PT ratio, and SOFA score and was highly predictive for 28-day mortality in the derivation study and associated with significantly better prediction of death compared to the ISTH's overt DIC classification in a derivation cohort of 332 sepsis patients who were suspected to have DIC [67,68]. Similarly, the SIC diagnostic criteria were found to be more feasible in the detection of appropriate candidates for anticoagulation, compared to the ISTH overt DIC criteria and Japanese Association for Acute Medicine (JAAM) DIC criteria, while a retrospective study by Ding et al. found no relevant difference between SIC score and ISTH's overt DIC score in a similar in-hospital population [69,70]. Similarly, Japanese JAAM criteria for DIC take into account parameters such as platelet count, FDP and fibrinogen concentrations, PT ratio, and systemic inflammatory response (SIRS) criteria [71]. Recently, it has been shown that the use of scores such as JAAM and ISTH could aid in the early identification of septic DIC and initiation of therapies such as recombinant thrombomodulin and/or antithrombin III that were associated with the reduction in in-hospital mortality [72]. Finally, assays based on viscoelastic tests that utilize whole-blood samples provide more precise insight on coagulation status in sepsis by assessing clot formation and dissociation as well as the contribution of both plasmatic and cellular components of the hemostatic system [73]. Table 1 shows parameters required to calculate a score according to the ISTH overt DIC and SIC diagnostic systems.

3.2.4. *When to suspect disseminated intravascular coagulopathy in a patient with septic shock*

Patients who develop DIC can present with both thrombosis and bleeding, either as separate phenomena or together. The severity of this

Table 1
Overt DIC criteria by ISTH and SIC criteria for coagulopathy in sepsis.

		ISTH overt DIC	SIC criteria
Variable	Points	Range	Range
Platelet count, *x10^9/L*	2	≤50	<100
	1	50–100	100–150
	0	≥100	<100
Prothrombin time, *s* Prothrombin ratio	2	≥6	>1.4
	1	3–6	>1.2–≤1.4
	0	≤3	≤1.2
Fibrinogen, *mg/dL*	1	≤100	–
	0	≥100	–
D-dimer or FDP	3	Strong increase	–
	2	Moderate increase	–
	0	No increase	–
Symptoms and underlying disorder known to be associated with DIC	–	Required in order to diagnose DIC	–
SOFA score, *points*	2	–	≥2
	1	–	1
Total score for overt DIC or SIC		**≥5 points**	**≥4 points**

Abbreviations: DIC-disseminated intravascular coagulation; **FDP**-fibrin degradation products; **ISTH**-International Society on Thrombosis and Hemostasis; **SIC**-sepsis-induced coagulopathy; **SOFA**-sequential organ failure assessment.

thrombohemorrhagic syndrome ranges from asymptomatic to life-threatening [74]. In the initial hypercoagulable state, the deposition of fibrin thrombi in the microvasculature leading to development of thrombosis, embolism and microvascular occlusion, may cause tissue ischemia and/or infarction. Subsequently, multiorgan dysfunction can occur, which foremost seems to affect the lungs and kidneys. However, since clot deposition takes place throughout the vasculature in this acquired disorder, other organs such as the brain, heart, liver, spleen, pancreas and the gastrointestinal tract can also be affected [75,76]. The clinical presentation of the thromboembolic state may vary from manifest thromboembolic disease to widespread microthrombosis mainly presenting as organ dysfunction. Once platelets are depleted, coagulation factors consumed and there is an increased plasmin formation, bleeding may occur. A similar range in severity applies to the hemorrhagic state, from minor bleedings only appearing when there is a trauma to widespread major bleeding in various sites and organs. The occurrence of thrombosis in small and midsize vessels dominates the clinical picture in most patients, whereas major bleeding as the unique clinical presentation only appears in a minority of DIC patients (5–12% in previous studies) [77,78]. Concomitant occurrence of shock is common in sepsis-induced DIC [79]. Multiple clinical manifestations may appear due to the non-localized affection of the vasculature. Nonetheless, general malaise, mental dysfunction, petechiae, hypotension and cutaneous, mucosal and/or internal hemorrhage are particularly common presentations. Taken together from a clinical point of view, sepsis-associated DIC should be suspected in patients with signs of severe infectious disease, thrombosis and/−or bleeding-related symptoms, dysfunction of any organ and presence of related laboratory abnormalities (low/decreasing platelet count, prolonged global coagulation tests (PT, aPTT), low plasma levels of coagulation factors and increased markers of fibrin formation and/or fibrin degradation products (e.g. D-dimer).

3.2.5. *Principles of management*

DIC cannot be resolved without treatment of the underlying disorder, which is considered the keystone in the management of the syndrome. Hence, in patients with sepsis-induced DIC, the cause of the infection must be addressed and treated with the appropriate therapy, e.g. antibiotics or surgery, for the DIC-related symptoms to disappear. There may, however, be a delay in the replenishment of blood components during recovery from the infection. Depending on the degree of coagulopathy, supportive treatment to stabilize the coagulation system may therefore also be necessary. The supportive strategy is individual and depends on whether thrombosis or bleeding dominate the clinical picture. In patients with active bleeding, administration with blood components in the form of platelets or plasma have clearly been shown to be effective, which also applies to those patients at increased risk of bleeding in need of an invasive procedure [80]. However, prophylactic use of platelet concentrates or plasma have failed to demonstrate any beneficial effect in those patients without current bleeding or without increased risk of bleeding [81]. The use of plasma to correct coagulation factor deficits may be complicated by the large volumes of plasma required, hence coagulation factor concentrates constitute a more suitable alternative for some patients. To be noted, however, is the lack of some coagulation factors, e.g. factor V, in factor concentrates and that in DIC there is typically a deficit of all coagulation factors. The previous perception that small traces of activated coagulation factors in prothrombin complex concentrates potentially may worsen the coagulopathy, does not seem to apply significantly to current-generation concentrates [82]. When deficits concern specific coagulation factors, there are certain purified products that can be used to correct deficiencies, e.g. fibrinogen [83]. Vitamin K also can be used to increase the level of vitamin K-dependent coagulation factors [84].

Current recommendations state that platelet transfusion should be considered in patients with DIC who are bleeding or at high risk of bleeding, where they have a platelet count $<50 \times 10^9$/l (L). Similarly, plasma or coagulation factor concentrates are recommended to patients with DIC who are bleeding or at high risk with a prolonged PT (>3 s) and/or hypofibrinogenemia (<1.5 g (g)/L) [84]. The flowchart of therapeutic strategy in patients with sepsis-induced DIC is reported in Fig. 4.

4. Effects of antithrombotic therapy during sepsis

4.1. *Effects of antiplatelet drugs on sepsis*

Given that platelets contribute to the thrombotic and inflammatory response during sepsis, it is logical that drugs reducing platelet reactivity might influence outcomes.

Commonly used antiplatelet agents include the cyclo-oxygenase inhibitor aspirin, and $P2Y_{12}$ inhibitors, including clopidogrel, prasugrel and ticagrelor.

The effects of both aspirin and $P2Y_{12}$ inhibitors during experimental human models of sepsis have been characterized. In healthy volunteers undergoing intravenous injection of bacterial endotoxin, $P2Y_{12}$ inhibition reduces the release of cytokines such as TNF α and IL-6, whilst aspirin potentiates this [17,22]. How these divergent actions translate into effects on clinical outcomes remains to be fully understood [85,86].

Observational data have suggested that antiplatelet drugs may reduce sepsis-associated mortality. For example, a nationwide population-based cohort study including 683,421 patients with sepsis showed that treatment with an antiplatelet drug, mainly aspirin, was associated with significantly lower in-hospital mortality compared to no antiplatelet drug [adjusted odds ratio (OR) 0.82, 95% confidence interval (CI) 0.81 to 0.83] [87].

However, in a prospective setting this has not been observed. The ANTISEPSIS substudy of the Aspirin in Reducing Events in the Elderly (ASPREE) trial included 16,703 participants receiving aspirin 100 mg once daily or placebo for a median of 4.6 years. There was no evidence of a difference in sepsis associated mortality between the groups [hazard ratio (HR) 1.08, 95% CI 0.82 to 1.43, aspirin vs placebo] [88].

There are few studies comparing those receiving vs. not receiving a $P2Y_{12}$ inhibitor during sepsis and related conditions. A double-blind randomized trial of ticagrelor or placebo in patients with pneumonia showed that the active drug led to significantly lower levels of platelet-leukocyte aggregates and neutrophil extracellular traps [89]. Moreover, ticagrelor significantly reduced requirement for supplemental oxygen, and there were trends towards more favorable spirometry parameters

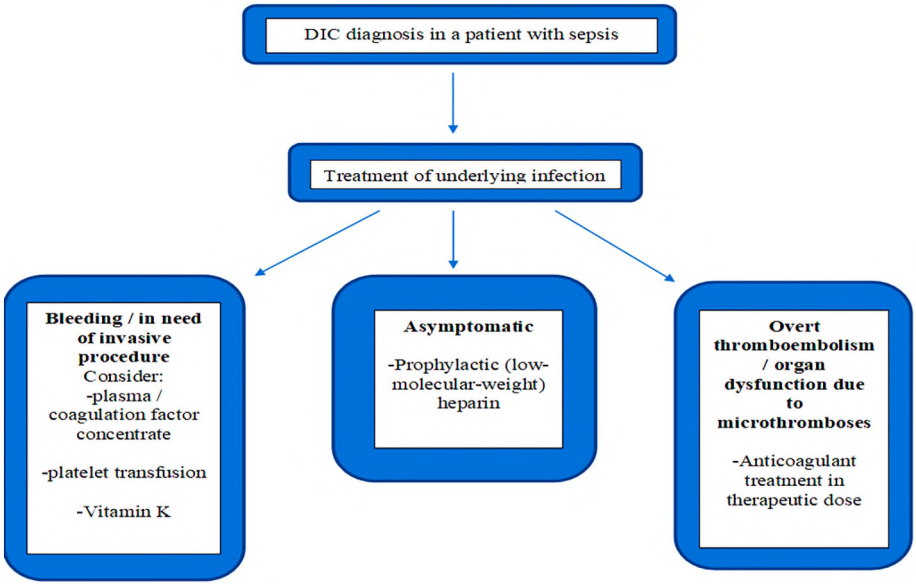

Fig. 4. Flow-chart of therapeutic strategy in sepsis-induced DIC.

when receiving ticagrelor. However, effects on important endpoints such as mortality have not been reliably tested. When comparing between $P2Y_{12}$ inhibitors, in the PLATelet inhibition and patient Outcomes (PLATO) study, which randomized 18,624 aspirin-treated participants with a diagnosis of acute coronary syndrome (ACS) to receive either ticagrelor or clopidogrel, there was a significantly lower mortality rate following pulmonary infection or sepsis occurring in the group receiving ticagrelor [90]. A recent meta-analysis including 36,514 patients from 10 trials showed that ticagrelor significantly reduced the incidence of pneumonia [relative risk (RR) 0.80, 95% CI 0.67–0.95], though not other infections or sepsis [91]. There are several plausible explanations that might contribute to this finding, considering that the outcome of sepsis events is a fine balance between appropriate and dysregulated aspects of the immune response. Ticagrelor is a more potent and reliable $P2Y_{12}$ inhibitor than clopidogrel [92], and therefore reduces the intensity of the inflammatory response as seen in experimental endotoxaemia. Pleiotropic effects of either ticagrelor, which may, for example, potentiate adenosine-induced neutrophil chemotaxis and phagocytosis [93]; or clopidogrel, which may suppress leukocyte count through an as yet undetermined mechanism [90], might also contribute. Direct antimicrobial effects of ticagrelor on gram-positive but not gram-negative bacteria have also been demonstrated [94], and the risk of gram-positive infections was lower than when receiving clopidogrel in a retrospective study of ACS patients (HR 0.37, 95% CI 0.22 to 0.63) [95].

Any role in sepsis of other $P2Y_{12}$ inhibitors such as prasugrel and cangrelor has not been well studied. Similarly, few studies have included GP IIb/IIIa inhibitors (such as abciximab, eptifibatide and tirofiban) though a recent small trial co-administrated eptifibatide with the prostacyclin analogue iloprost in sepsis and demonstrated reduced platelet consumption, fibrin turnover and improved endothelial function compared to placebo [96].

4.2. *Anticoagulant treatment in severe sepsis*

The benefit of prophylaxis for venous thromboembolism (VTE), usually provided by low-molecular-weight heparin, is well established in critically ill patients [97]. Unfractionated heparin (UFH) possesses both anticoagulant and immunomodulatory effects and it has been considered whether heparin can improve clinical outcomes in patients with severe sepsis developing uncontrolled immunothrombosis. However, heparin's exact therapeutic role in patients with sepsis remains to be determined [98]. Some evidence for heparin therapy in patients with severe sepsis came from the phase III trial of antithrombin III (ATIII) vs placebo, KyberSept [99]. In those not receiving antithrombin III, there was evidence of an association between use of thromboprophylactic UFH and lower 28-day mortality (36.6% [heparin] vs. 43.6% [no heparin]). Similarly, the placebo groups of the PROWESS trial of activated protein C (APC) (28% [UFH] vs. 39% [no UFH] and the OPTIMIST trial of tissue pathway factor inhibitor (29.8% [UFH] vs. 42.7% [no UFH]) demonstrated similar trends [100–102]. However, as these were non-randomized, non-significant subgroup analyses, caution in interpretation should be exercised. Furthermore, in 2008, Zarychanski et al. reported a retrospective analysis showing lower 28-day mortality when receiving therapeutic-dose UFH vs. no UFH in 695 patients with septic shock (44.2% vs. 40.1%, HR 0.85 [95% CI 0.73–1.00], $p = 0.05$), even greater in the quartile with the highest APACHE II scores [103]. The following year, the HETRASE study, a prospective randomized double-blind study, was reported. 319 sepsis patients were randomized to either intravenous UFH (500 units/h) or placebo but no significant differences in the primary endpoints of length of stay in surviving patients nor multiorgan dysfunction score. Similarly, there was no significant benefit in 28-day mortality (14% [UFH] vs. 16% [placebo], OR 0.87 [0.44–1.69, $p = 0.65$). Explanations for the negative results in the HETRASE study, may be a less-severely ill study population as well as choice of primary endpoint [98]. As patients with the most severe sepsis are the group that might be expected to benefit the greatest from heparin, a clinical trial focusing on patients with septic shock investigating dosing of therapeutic UFH, compared to standard-of-care VTE prophylaxis, is warranted to clarify the role of heparin in the severest sepsis cases. This is now being assessed in the Heparin Anticoagulation in Septic Shock (HALO) study (NCT03378466). Heparin has advantages of a well-characterized safety profile and relatively low cost. Whilst there is some specific evidence for the role of LMW heparins in the reduction of mortality from severe sepsis, this has not been well studied [104]. Therapeutic dose parenteral anticoagulation should be considered in patients presenting with clinically overt thromboembolism [84].

4.3. *Treatment with endogenous coagulation inhibitor concentrates*

Stabilization of the levels of physiological anticoagulants has been evaluated in numerous studies. The activity of a key endogenous anticoagulant, ATIII, is reduced in septic patients with DIC, mainly due to vascular leakage and factor consumption [105]. Clinical trials investigating the efficacy and safety of supraphysiological dosing of ATIII in

sepsis patients, have, to this date, failed to demonstrate a significant reduction in mortality [106]. However, posthoc analyses from the KyberSept study, including only sepsis patients with DIC, suggested both improved organ function and lowered mortality when receiving ATIII compared to placebo (e.g. 28 day mortality 25.4% vs. 40.0%, RR 0.64, 95% CI 0.43 to 0.94, $p = 0.024$) [107]. This has also been supported by retrospective data from Japan and some meta-analyses [106,108]. Nevertheless, evidence of beneficial effects on survival for ATIII in sepsis patients with DIC remains to be determined prospectively [106]. Supplementation therapy with ATIII is approved in Japan but not commonly used elsewhere [109].

Activated protein C (APC) has, in conformity with antithrombin, been evaluated in clinical trials and been suggested to reduce mortality in the more severely ill septic patients. In 2007, however, a meta-analysis of prior studies concluded that clinical advantages were lacking and a subsequent clinical trial evaluating recombinant human activated protein C in patients with septic shock, the PROWESS-SHOCK study, was even terminated in advance due to absence of any beneficial effects of the drug, leading to withdrawal of APC from the market [110,111].

Recombinant soluble thrombomodulin (rTM) exerts its anticoagulant effect by activating protein C via modulation of thrombin's mechanism of action. Previous data from both retrospective studies and clinical phase II trials have indicated beneficial effects of rTM but have failed to demonstrate a significant mortality reduction [108]. A phase III clinical trial incorporating critically ill sepsis patients with organ failure and coagulopathy was therefore performed. The SCARLET trial was a randomized double-blind placebo-controlled multicenter trial of 816 patients with sepsis and coagulopathy, but similarly demonstrated no significant reduction in 28-day mortality when receiving rTM compared to placebo (26.8% vs. 29.4%, $p = 0.32$). [112]. Administration of rTM has been approved in Japan since 2008 but not elsewhere [109].

No head-to-head comparison between ATIII and rTM has so far been performed. However, in 2015 Murata et al. concluded, based on retrospective analyses from Japanese administrative data, that no significant difference in 28-day mortality was seen in sepsis patients with DIC between the two agents [113].

5. Conclusions and future directions

Despite recent sepsis guidelines recommending early diagnosis and timely initiation of therapy, sepsis still remains an open challenge worldwide. Sepsis is a complex and life-threatening disease in which inflammatory systems, concomitant uncontrolled complement activation, coagulation, and platelet dysfunction lead to tissue damage and organ dysfunction. Whether thrombocytopenia is a cause or a consequence of the severity and progression of sepsis is still unknown. However, the critical role of thrombocytopenia in sepsis is emphasized by the fact that platelet count is included in the SOFA score and is strongly associated with an increased risk of mortality. Although aspirin appears to be promising in patients with sepsis, the potential beneficial effect of antiplatelet therapies in these patients needs further studies.

Coagulopathy commonly occurs in sepsis and can progress to DIC, which is an independent predictor of mortality. In fact, the abbreviation DIC is often considered by many clinicians to mean “death is coming.” In this context, making a timely diagnosis of the coagulation disorder and initiating early, targeted therapy is important to improve the management and overall survival of patients with sepsis.

In the near future, the diagnostic and prognostic role of thromboelastometry/elastography (ROTEM/TEG) in patients with sepsis should be further investigated. These methodologies have the advantage of being easy to use and can rapidly investigate the intrinsic and extrinsic coagulation pathway separately and the contribution of platelets and fibrinogen to clot formation. In addition, a recent meta-analysis of 11 observational studies of adult patients with sepsis shows that certain viscoelastic parameters of ROTEM/TEG are associated with an increased risk of mortality [114]. With this in mind, these simple point-of-care rapid tests may help clinicians to choose the correct clinical monitoring of the patient or to evaluate the most appropriate diagnostic and therapeutic strategies throughout the course of the disease. Similarly, in the coming years, additional evidence will be needed to assessing the critical role of glycocalyx integrity and function in patients with sepsis. Currently, there is emerging evidence that endothelial activation and damage are critical drivers in sepsis-associated coagulopathy and that the endothelium plays an important role in balancing hemostasis [115]. In this light, for example, determination of plasma concentrations of glycocalyx components might allow clinicians to assess disease severity, response to treatment, and prognosis in these patients.

In conclusion, sepsis-associated coagulopathy is common and is associated with an increased risk of mortality. Early identification of warning signs and rapid and optimal management of these patients are the two essential keys to improving patient survival. Further robust evidence will be needed in the coming years.

Practice points

- The link between inflammation and coagulation is close; virtually all patients with sepsis may have coagulation abnormalities.
- During sepsis, there is direct and indirect platelet activation, increased platelet reactivity and increased platelet release from the bone marrow. Indeed, drugs that reduce platelet reactivity may influence outcomes in these patients.
- Thrombocytopenia is common in sepsis, particularly in severe sepsis. Differential diagnosis should be performed to reduce potential other causes of reduced thrombocyte that could mimic sepsis-related thrombocytopenia.
- Disseminated intravascular coagulopathy is an acquired thrombohemorrhagic syndrome characterized by the dysfunctional systemic activation of coagulation pathways resulting in intravascular fibrin formation, microangiopathic thrombosis, and subsequent depletion of coagulation factors and platelets.
- Making a timely diagnosis of the coagulation disorder and initiating early, targeted therapy is important to improve the management and overall survival of patients with sepsis.

Research agenda

- The effects of aspirin and $P2Y_{12}$ inhibitors, particularly prasugrel and cangrelor, on clinical outcomes of sepsis remain to be fully understood.
- Determining the mechanism behind thrombocytopenia in sepsis.
- Establish a practical approach for the management of DIC in addition to initial treatment of the underlying disease.
- Further studies are needed to assess the role of antithrombin and recombinant thrombomodulin in sepsis patients with DIC.

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Declaration of Competing Interest

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