Management Strategies in Septic Coagulopathy

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One of the ‘organs’ that can be affected by sepsis is the coagulation system. Coagulopathy in sepsis may take the form of sepsis-induced coagulopathy (SIC) or sepsis-associated disseminated intravascular coagulation (DIC). It is important to identify SIC early, as at this stage of coagulopathy anticoagulants may be of the greatest benefit. The mainstream management strategies in septic coagulopathy include the causal treatment of sepsis, unfractionated heparin, low-molecular-weight heparin, antithrombin, and recombinant human thrombomodulin. The last two have been associated with the highest survival benefit. Nevertheless, the indiscriminate use of these anticoagulants should be avoided due to the lack of mortality benefit and increased risk of bleeding. The early diagnosis of SIC and monitoring of coagulation status during sepsis is crucial for the timely management and selection of the most suitable treatment at a time.

antithrombin coagulopathy disseminated intravascular coagulation heparin management sepsis thrombomodulin treatment

1. Introduction

Sepsis is defined as ‘a life-threatening organ dysfunction caused by a dysregulated host response to infection’ [1]. Septic shock is defined as a subtype of sepsis, with hemodynamic and metabolic abnormalities, and is associated with increased mortality [1]. One of the ‘organs’ that can be affected by sepsis is the coagulation system.

Coagulopathy in sepsis may take the form of sepsis-induced coagulopathy (SIC) (early stage) [2] or sepsis-associated disseminated intravascular coagulation (DIC) (late stage). Disseminated intravascular coagulation is defined by the International Society on Thrombosis and Hemostasis (ISTH) as ‘an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which, if sufficiently severe, can produce organ dysfunction’ [3]. These two clinical syndromes differ in pathophysiology. A major role in the pathophysiology of SIC is attributed to decreased fibrinolysis, caused by the overproduction of plasminogen activator inhibitor-1 (PAI-1), leading to hypercoagulation [4]. It is important to identify SIC early because anticoagulants at this stage may be of the greatest benefit. The transition from SIC to overt sepsis-associated DIC is associated with the massive consumption of coagulation factors and platelets; hence, bleeding complications occur, and anticoagulants at this stage may be of no benefit [5]. Recommendations regarding the management of SIC/sepsis-associated DIC differ between organizations [6][7]. There are several management strategies that can be employed in patients with SIC

and sepsis-associated DIC. This topic is an area of active research, with a great number of new publications in the last 5 years.

2. Management Strategies in SIC and Sepsis-Associated DIC

2.1. Causal Treatment of Sepsis

The British guidelines for the diagnosis and management of DIC state that 'the cornerstone of the treatment of DIC is treatment of the underlying condition' [8]. Early antibiotic therapy is the key therapy in sepsis patients. The Surviving Sepsis Campaign (SSC) guidelines recommend the administration of an antimicrobial agent within an hour of diagnosis of sepsis or septic shock. Empiric broad-spectrum antimicrobial therapy may differ depending on the most common microbes and their resistance patterns in the local setting—the so-called microbiological map [6]. The newest edition of the SSC guidelines published in 2021 upgraded the importance of infection source control. If the source of infection is amendable to removal, it should be removed as soon as it is logistically possible. If the probable source of infection is a vascular line, alternative vascular access should be secured, and the vascular line that is the probable source of infection should be removed immediately [6].

Another key therapy in the management of sepsis patients is fluid resuscitation. The most recent edition of the SSC guidelines downgraded the importance of the initial fluid bolus of 30 mL/kg of balanced crystalloid, paying more attention to fluid responsiveness measured with dynamic methods [6].

2.2. Unfractionated Heparin (UFH)

It is important to mention that UFH in sepsis patients may have much more than only anticoagulant effects. Heparin has various immunomodulatory properties: It inhibits lung inflammation via the inactivation of NF-κB [9], in addition to inhibiting neutrophil recruitment [10] and LPS-induced inflammatory mediators [11], and it binds to histones [12]. Heparin may also protect glycocalyx from shedding [13][14]. The most recent study analyzing the effect of UFH in patients with SIC was performed in 2014 [15]. In this small (n = 37), prospective clinical study, the dose of UFH was 70 u/kg/24 h as a continuous infusion, and the dose was adjusted to aim for 2–3-fold prolongation of activated partial thromboplastin time (aPTT). The intervention drug decreased the hypercoagulable state, as judged by the concentration of prothrombin fragments 1 and 2 (F1 + 2) and thrombin-antithrombin complexes (TATs), the time of mechanical ventilation, and hospitalization in the ICU. The retrospective analysis of a large database of SIC (ISTH) patients performed in 2022 showed that UFH given subcutaneously or via continuous intravenous infusion, in prophylactic or therapeutic doses, reduced 28-day mortality (hazard ratio (HR) 0.32, 95% CI 0.26–0.41, $p < 0.001$) and hospital mortality (HR 0.38, 95% CI 0.31–0.47, $p < 0.001$), with a favorable safety profile in the context of intracranial and gastrointestinal hemorrhage [16]. Another retrospective analysis of a large database showed that early administration of UFH in prophylactic doses (at least five doses) was associated with decreased in-hospital mortality (HR 0.70, 95% CI 0.56–0.87, $p < 0.001$) [17].

2.3. Low-Molecular-Weight Heparin (LMWH)

Some of the newest reports regarding the potential superiority of LMWH over UFH for prophylaxis and treatment of SIC come from the experience gained during the novel coronavirus disease (COVID-19) pandemic. A retrospective analysis of COVID-19 patients showed that the 28-day mortality of patients with SIC scores (ISTH) of ≥4, who received LMWH, was lower in patients who did not receive LMWH (40.0 vs. 64.2%, $p = 0.029$) [18]. Moreover, the recently concluded HEP-COVID randomized clinical trial enrolled COVID-19 patients with increased D-dimer concentration or SIC scores of ≥4 to examine the difference between therapeutic dose, intermediate dose, and standard prophylactic LMWH dose subgroups [19]. The primary outcome was venous or arterial thromboembolism or death from any cause. The principal safety outcome was major bleeding at 30 days. In the subgroup of patients treated with the therapeutic-dose LMWH, a reduction in thromboembolism was noted (0.37 (95% CI 0.21–0.66, $p < 0.0001$)). Overall, the results showed that the therapeutic dose compared with the prophylactic dose reduced the occurrence of thromboembolism and death without increasing major bleeding among COVID-19 inpatients with increased SIC scores; however, these observations were only shown in the non-ICU population [19].

2.4. Antithrombin (AT)

Antithrombin is a potent physiological anticoagulant. Moreover, AT binds to heparan sulfate present in the glycocalyx layer [20][21]. The most recent Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock suggest the use of AT in patients with sepsis-associated DIC whose AT activity is ≤70% [22]. This suggestion was based on four studies, one of which showed reduced mortality [23], while the other three showed no effect on mortality with improvement in DIC scores [24][25][26]. The problem with studies on the pharmacological treatment of sepsis-associated DIC is that not all studies accurately identified DIC patients; hence, the beneficial effect might not be shown [27][28]. In 2016, the inverse probability of the treatment-weighted propensity score analysis on 1784 patients diagnosed with DIC showed a statistically significant association between AT supplementation and lower in-hospital all-cause mortality (OR 0.75, 95%CI 0.57–0.98, $p = 0.034$) [29]. In 2018, the results of a network meta-analysis in patients with sepsis-associated DIC were published. The authors compared four different anticoagulants and a placebo. The results showed that AT compared with the placebo was associated with a five-fold higher likelihood of sepsis-associated DIC resolution (OR 0.20, 95% credible intervals 0.05–0.81) [30]. In 2019, Tanaka et al. published the results from a nationwide registry study on the use of AT in sepsis-associated DIC. Almost 3000 patients in the registry had mostly abdominal origin of sepsis, and most of them required vasopressors. Although the analysis of all the included patients did not show any effect of AT on in-hospital mortality, the subanalysis of patients diagnosed with sepsis-associated DIC (ISTH criteria) demonstrated an independent association between AT and/or recombinant human thrombomodulin (rhTM) and lower in-hospital mortality than other anticoagulants (HR 0.74 (95% CI 0.60–0.92) [31]. A post hoc subgroup analysis of these registry data showed survival benefits for the use of AT without concomitant heparin in sepsis patients with higher predicted mortality and most severe coagulopathy [32]. As far as the optimal threshold for starting the AT therapy is concerned, in-hospital mortality was significantly reduced only in patients with very low antithrombin activity ≤43% (adjusted HR 0.60, 95%CI 0.37–0.99; $p = 0.045$) [33]. The therapeutic goal for AT supplementation was activity ≥70%, optimally 80% [34].

2.5. Activated Protein C (APC)

Performed in 2011, the PROWESS SHOCK study aimed to evaluate the initial promising results of its predecessor, the PROWESS trial. It was supposed to assess the clinical effectiveness and safety of APC, the only novel anti-sepsis agent to successfully complete the phase 3 trial [35]. However, this follow-up study showed no effect of APC in reducing the risk of death in sepsis patients. Moreover, the use of APC was associated with a higher risk of bleeding, with RR 1.45 (95% CI 1.08–1.94, $p < 0.05$), and no effect on the risk of any other serious adverse event (RR 1.04, 95% CI 0.92–1.18, $p < 0.05$) [35]. This evidence resulted in taking the potentially immunomodulating agent off the market [36].

2.6. Thrombomodulin (TM)

Thrombomodulin is an endothelial anticoagulant cofactor promoting the thrombin-mediated activation of protein C [37]. In the SCARLET trial, investigators defined septic-associated coagulopathy (SAC) as INR > 1.4, with no other explanation for this abnormality than sepsis, thrombocytopenia in the range 30–150 × 10^9/L or >30% platelet decrease in 24 h, and respiratory or hemodynamic dysfunction. In this randomized, controlled trial (RCT), patients were randomized to receive a bolus of rhTM or a placebo for 6 days. The 28-day all-cause mortality did not differ significantly between the intervention and the placebo groups (26.8% vs. 29.4%, $p = 0.32$). However, the post hoc analysis of the SCARLET trial suggests that patients who had features of SAC at the time of administration of the first dose of rhTM and did not receive heparin may benefit from it [38]. Another post hoc subgroup analysis of the same trial showed that absolute risk reduction was greater in patients with higher baseline thrombin generation biomarker concentration (F1 + 2 or TAT) [39]. An analysis of three multicenter observational studies showed that rhTM was associated with a lower rate of 28-day mortality (adjusted risk difference RD—17.8% (95% CI—28.7 to—6.9%)) and in-hospital mortality (adjusted RD—17.7% (95% CI—27.6 to—7.8%)), but only in sepsis patients with a high concentration of D-dimers (Me 51900 (IQR 35200–113000) ng/mL) and fibrin degradation products (Me 120200 (IQR 79200–266000) ng/mL). The study was interesting because four coagulation phenotypes of sepsis were identified based on the laboratory parameters of hemostasis: severe sepsis and severe coagulopathy, severe sepsis and moderate coagulopathy, moderate sepsis with coagulopathy, and mild sepsis without coagulopathy [40]. A post hoc analysis of patients with sepsis-associated DIC registered in a nationwide multicenter Japanese database showed that the combined therapy with AT and rhTM does not present additional benefits in terms of survival [41]. Another post hoc analysis from a post-marketing surveillance database from Japan showed that in patients with severe thrombocytopenia (<50 × 10^9/L) and AT deficiency (activity < 50%), the concomitant use of rhTM and AT reduced 28-day mortality (HR 0.62, 95%CI 0.39–0.98) [42].

2.7. Tissue Factor Pathway Inhibitor (TFPI)

A tissue factor pathway inhibitor is a plasma protease inhibitor that blocks the initiation phase of thrombin generation induced by the tissue factor (TF) [43]. The in vivo administration of recombinant TFPI (rTFPI) in experimental animal models prevented thrombosis and fibrin deposition on the subendothelial matrix, reduced mortality from Escherichia coli-induced sepsis, and protected against DIC development [44]. The elevated levels of TFPI have been found in patients with sepsis-associated DIC in conjunction with elevated TF levels, suggesting a relative deficiency of TFPI to neutralize the TF pathway activation. Since coagulation activation in sepsis-

associated DIC is primarily mediated through the TF/FVIIa pathway and the overexpression of TF compared with TFPI, the substitution of TFPI seems a rational treatment approach [44].

There is a paucity of new data regarding the use of TFPI in sepsis management, as most of the clinical trials come from the years 2000–2006 [45][46][47]. There are foundations for further investigation based on the role of endothelial cells in maintaining intravascular patency through their anticoagulant properties. Endothelial cells synthesize proteoglycans, a component of the glycocalyx, which bind and potentiate plasma anticoagulant proteins, including TFPI and AT [48]. Under inflammatory and septic conditions, endothelial cells lose their anticoagulant properties. Injury to endothelial cells and the destruction of the glycocalyx due to the suboptimal synthesis of TFPI may induce the activation of coagulation, accelerating the development of sepsis-associated DIC [49]. The study by Walborn et al. aimed to quantify endothelial function, including endogenous anticoagulants such as TFPI and protein C, in the plasma of patients with sepsis and DIC [50]. The researchers wanted to determine how these factors relate to the severity of illness and the outcome. In their study group, TFPI concentration was increased in patients with overt DIC (mean 110, SD ± 90), non-overt DIC (mean 104, SD ± 69) vs. no DIC (mean 95, SD ± 58), and healthy controls (mean 61, SD ± 19) ng/mL ($p < 0.05$). Further analysis showed higher TFPI concentration in the non-survivors; this result, however, was not statistically significant. The authors concluded that although TFPI did not show significant variation based on mortality, the increased concentration of TFPI in patients with sepsis and DIC, compared with healthy controls, may emphasize the role of endogenous anticoagulants in the disease process. The measurement of functional TFPI levels, in addition to protein levels, may provide further insight into the role of TFPI in sepsis-associated DIC [50].

2.8. Transfusion of Blood Components

The British guidelines for the diagnosis and management of DIC suggest that in patients with DIC, the transfusion of PLTs (trigger < 50 × 10^9/L) and/or fresh-frozen plasma (FFP) should be used if bleeding occurs or invasive procedures are planned. Moreover, if there are concerns with fluid overload, coagulation factor concentrates can be used (e.g., prothrombin complex concentrate, and fibrinogen concentrate). However, clinicians should bear in mind that DIC leads to the consumption of all coagulation factors [8]. A recent, prospective, open-label RCT in children with severe sepsis or septic shock showed that a combination of fresh-frozen plasma, low-dose heparin, and tranexamic acid was associated with better survival and prevented progression to overt sepsis-associated DIC, with no increase in bleeding [51].

2.9. Therapeutic Plasma Exchange (TPE)

In a prospective, randomized study, it was shown that TPE may outperform UFH in the treatment of patients with sepsis-associated DIC based on laboratory (e.g., markers of endothelial injury) and clinical (e.g., 28-day cumulative survival, acute kidney injury, acute respiratory distress syndrome, and bleeding events) outcomes. The possible mechanism is suggested to be improved endothelial function [52].

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