VIA MEDICA

REVIEWS

Anaesthesiology Intensive Therapy
2016, vol. 48, no 5, 352–359
ISSN 1642–5758
10.5603/AIT.a2016.0051
www.ait.viamedica.pl

Coagulopathy in sepsis — a new look at an old problem

Małgorzata Lipińska-Gediga

Department of Anaesthesiology and Intensive Care, 4th Military Hospital of Wrocław, Poland

Abstract

Sepsis is a life-threatening condition characterized by a systemic response to microbial infection. Despite considerable progress in intensive care medicine, the incidence of sepsis and the number of sepsis-related deaths are increasing world-wide. There is a complex relationship between the coagulation, immune and inflammatory systems in sepsis. Activation of the coagulation cascade in sepsis is a result of a pathogen invasion and is a part of a immuno-inflammatory host response. In sepsis, the close cooperation of the immune and coagulation systems through cross signalling results in immunothrombosis. According to a recently described new theory, immunothrombosis is a immune response in which the local activation of coagulation facilitates the recognition and destruction of pathogens. Small amounts of clot formation are beneficial for the host because of bacteria trapping and prevention of the systemic spread of infection. Sepsis is a dynamic syndrome and in all patients with sepsis coagulation changes may progress from a normal profile to hypercoagulability and hypofibrinolysis, hyperfibrinolysis, and ultimately hypocoagulability.

Anaesthesiology Intensive Therapy 2016, vol. 48, no 5, 352–359

Key words: sepsis, coagulopathy; immunothrombosis; neutrophil extracellular traps; thrombocytes; fibrinolysis

Sepsis is not a single disease, but a highly heterogeneous syndrome that is the net result of host and pathogen interactions [1]. According to the current Surviving Sepsis Campaign Guidelines, sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and a syndrome shaped by pathogen factors and host factors with characteristics that evolve over time [2]. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction. One of the criteria for sepsis are coagulation abnormalities with INR > 1.5 or aPTT > 60 s and/or thrombocytopenia with a platelet count < 100 G L^{-1} [2].

Coagulopathy is highly prevalent in septic patients and may range from moderate thrombocytopenia to advanced disseminated intravascular coagulation (DIC). Thrombosis plays a significant role in early immune response in sepsis. This defensive role of thrombosis is now referred to as immunothrombosis. Immunothrombosis includes TF, immune cells and thrombin, VIIa and Xa factors which generate clots. Microthrombi are antimicrobial matrices forming a physical barrier to the pathogen. Microthrombi create places that cumulate antimicrobial strategies regarding resident and recruited immune cells accelerating the recognition and destruction of pathogens [3]. However, if uncontrolled, immunothrombosis is a major source of the pathologies associated with sepsis and thrombosis [3].

MECHANISM OF SEPSIS ASSOCIATED HAEMOSTATIC ABNORMALITIES

The microorganism and its derivatives drive the following changes:

a. monocytes-macrophages aberrant expression of tissue factor,
b. the impairment of anticoagulant pathways (antithrombin, protein C pathway, TFPI), caused by dysfunctional endothelial cells (ECs),
c. the overproduction of PAI-1(plasminogen activator inhibitor-1) by ECs and thrombin-mediated activation of thrombin-activatable fibrinolysis inhibitor (TAFI) resulting in the suppression of fibrinolysis [4].

Hemostasis and inflammation are closely tied and can regulate each other when activated during infection. The eradication of the invading pathogen depends on

the coagulative and the inflammatory responses of the host. In sepsis, the haemostatic balance is shifted toward a pro-coagulation state. The coagulation cascade is mediated by TF expression on monocytes, macrophages and by TF-expressing microparticles from platelets, monocytes and macrophages [5].

Monocytes and neutrophils are activated when they detect pathogen-associated molecular patterns (PAMPs) and/or damage-associated molecular patterns (DAMPs) [6]. These elements are recognized via pattern recognition receptors (PRRs), with Toll-like receptors (TLRs) and the complement receptors involved. The PRRs activate the coagulation system through increased production of TF and by impairment of anticoagulation and fibrinolysis [7]. TF-expressing microparticles from platelets, monocytes, and endothelial cells initiate the coagulation cascade, with a concomitant sharp decrease of TFPI (Tissue Factor Pathway inhibitor), which is a major inhibitor of TF-FVIIa-initiated coagulation [8]. In addition to PAMPs, alarmins (histones, nucleosomes, $HMGB_1$) originating from damaged host cells are also coagulation triggers. Cytokines such as TNF-α, IL-1, IL-6 are up-regulated after TF expression and influence natural anticoagulant suppression and endothelial damage. TF triggers the coagulation-independent signalling pathway mediated by PARs on immune cells. PAR-dependent signals induce pro- and anti-inflammatory pathways regulating the migration and proliferation of immune cells, as well as endothelial adhesion [9] (Fig. 1).

In $HMGB_1$ released after tissue damage all cysteines are in reduced form and this form of $HMGB_1$, while this form of $HMGB_1$ recruits leucocytes to the site of injury without stimulating cytokine release. Histones are DNA-binding proteins with a positive charge and are the most abundant proteins in the nucleus. Histones are classified as a new class of DAMPs while extracellular histones stimulate the migration of neutrophils, the aggregation of platelets and endothelial cell damage [8]. The procoagulant reaction is partially reversed by an increased temporal expression of tPA which is quickly inhibited by increased levels of PAI-1. The increase of TAFI activity results in amplifying the thrombogenic pathway. During sepsis, inflammation-induced coagulation results in excessive thrombin formation. Thrombin is an important platelet agonist via protease activated receptor (PAR)1, PAR3 and PAR4, present on the platelet membrane [8]. Platelets activation accelerates thrombosis. Platelet P-selectin expression increases monocyte TF expression and platelet adhesion to leucocytes and the endothelium. Platelets adhered to the endothelium and leucocytes create a surface for thrombin generation [5].

In response to pathogen stimuli, TLR4 of activated platelets has been shown to bind to neutrophils causing the secretion of nuclear content resulting in NET (Neutrophil extracellular trap) formation [10]. NETs include web-like structures of DNA, histones, neutrophil elastase, and myeloperoxidase able to entrap and kill microbes [3, 4], while

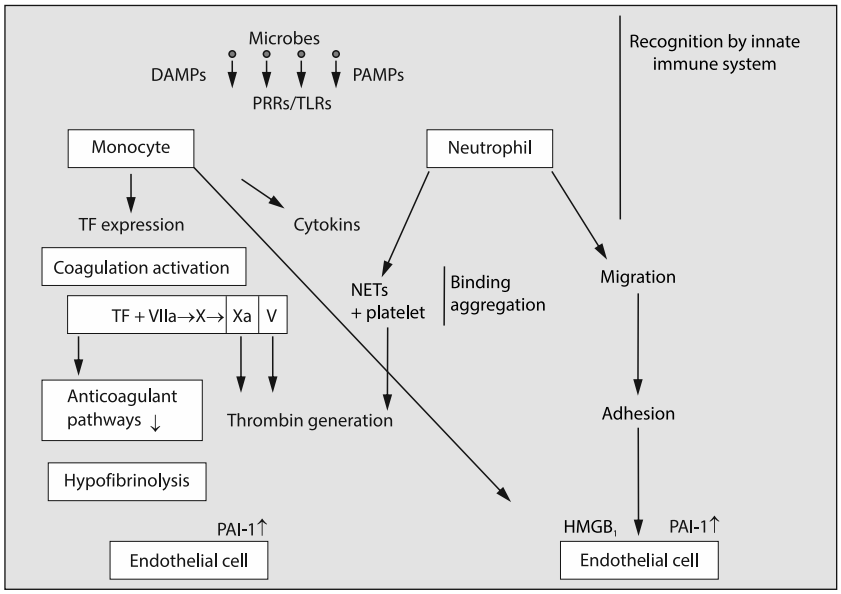

Figure 1. Coagulation in sepsis, immunothrombosis. PAMPs and DAMPs trigger TF expression on monocytes and NET release by neutrophils. NETs create places for platelet binding and aggregation

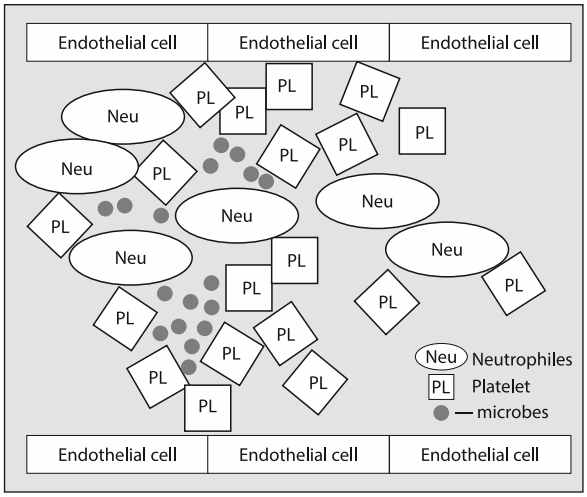

Figure 2. Immunothrombosis. Microthrombi with platelets and neutrophils. NETs +trapped pathogens

revealing proinflammatory and prothrombotic properties [4]. NETs activate factor XII, inactivate TFPI and provide places for platelet binding and aggregation [6]. NETs have been shown to intercalate within a fibrin clot and form a structural network that is resistant to lysis [6]. TF-mediated and NET-mediated immunothrombosis is a significant factor in early, innate immune response against bacterial spreading, facilitating the recognition and destruction of pathogens, but may lead to DIC, if uncontrolled [6] (Fig. 2).

Sepsis-associated haemostatic abnormalities range from the subclinical activation of blood coagulation to acute DIC, characterized by widespread microvascular thrombosis, the consumption of platelets and coagulation proteins, eventually causing bleeding. Sepsis-attributed mortality is as high as 30–50%, rising up to 70% in patients with an overt DIC [11].

UTILITY OF TEG/ROTEM MEASUREMENTS IN SEPTIC COAGULOPATHY

A reliable assessment of haemostatic status in sepsis may be provided by thromboelastography (TEG) [12], or thromboelastometry (ROTEM). Both rotational thromboelastography (TEG) and thromboelastometry (ROTEM) are point-of-care tests, which evaluate whole-clot formation and dissolution. To describe these viscoelastic changes, both systems have their own terminology. The main parameters are reaction time (R)(TEG) or clotting time (CT) (ROTEM), which is the period from the initiation of the test until the beginning of clot formation and which depend on concentrations of coagulation factors/inhibitors. Moreover, K-time or clot formation time (CFT) (TEG/ROTEM) is the period from the start of clot formation until the curve reaches an amplitude of 20 mm and reflects the propagation of clot formation. The kinetics of fibrin formation and cross-linking are expressed by the α-angle. Clot strength is represented by the maximal amplitude of the trace. The degree of fibrinolysis is reflected by the difference between the maximal amplitude and the amplitude measured after 30 and/or 60 min [13].

Adamzik *et al.* [14] revealed in a cohort study of 98 septic patients that the presence or absence of a single pathological thromboelastometry finding is associated with differences in survival. Although thirty-day survival was 85.7% when all thromboelastometry variables were normal, this comprised 58.7% when at least one variable was pathological ($P = 0.005$). A multivariate analysis revealed that the absence or presence of at least one pathological thromboelastometry variable allows for better prediction of 30-day survival in severe sepsis than the SAPS II and SOFA scores (OR 4.1; $P = 0.01$), respectively [14]. Septic patients who were hypocoagulable with a prolonged reaction time (R), reduced α angle or decreased maximum amplitude (MA) had increased mortality [13].

THE FIBRINOLYTIC SYSTEM AND ITS ROLE

Hemostasis is controlled by the fibrinolytic system, with plasmin as the key enzyme. Plasmin is generated from plasminogen by activators such as tPA and urokinase plasminogen activator (uPA), while the main inhibitor of tPA and uPA is PAI-1 (plasminogen activator inhibitor-1) [15]. Sepsis is associated with impaired fibrinolysis as a result of an increase of PAI-1 concentration in plasma. The fibrinolytic system also seems to be involved in pathogen clearance. According to the theory of immunothrombosis, a small amount of clot formation is beneficial for the host as bacteria and DAMPs are trapped, thus preventing systemic spread of infection [7, 16].

The hypercoagulability associated with hypofibrinolysis might be considered as an attempt to compartmentalize the infectious focus [11], and is followed by late fibrinolytic shutdown [17]. Savioli, in a study carried out in a group of patients with severe sepsis and septic shock, found that the coagulation and inflammatory response were unrelated with amount of organ failure and outcome, conversely inhibition of fibrinolysis was associated with morbidity and mortality though it was observed in a fraction of study group [18].

The two main markers used to quantify fibrinolysis are PAI-1 and TAFI. The balance between tPA and PAI-1 regulates fibrinolytic activity and TAFI, as well as neutrophil elastase modulate fibrinolysis. Dynamic changes in these molecules' activity results in the impairment of fibrinolysis [19]. Entrapment of bacteria by fibrin at the site of infection may limit their capacity to disseminate into nearby tissues, organs, and systemic circulation and explains why although the

impairment of fibrinolysis has a protective role in early host defence [19], elevated levels of PAI-1 and TAFI observed in septic patients were related to multiorgan failure and may possess value as prognostic markers in septic shock [20]. In the a study by Koyama *et al.* [21] in which 77 patients with sepsis were enrolled, 37 (48.1%) developed overt DIC within five days of their ICU stay. Patients who developed overt DIC were more severely ill with a higher APACHE II score, maximum SOFA scores and 28-day mortality, compared with patients who did not develop overt DIC. On Day 0, there were marked increases in TAT (thrombin-antithrombin complex) and PAI-1, and decreases in PC, plasminogen and α_2-PI activities, which were particularly marked in patients with subsequent development of overt DIC. According to the authors, only TAT and PAI-1 at the baseline were significant predictors of 28-day mortality among the biomarkers that had good discriminative power for the development of overt DIC. Based on the best calculated cut-off values, cut-off points at the baseline were set at 18 ng mL^{-1} for TAT and 270 ng mL^{-1} for PAI-1. The Kaplan-Meier survival curve for patients with sepsis demonstrated that TAT > 18 ng mL^{-1} and/or PAI-1 > 270 ng mL^{-1} on admission were significantly correlated with higher mortality ($P = 0.0024$) [21].

THE ROLE OF PARS , PROTEIN C , THROMBOMODULIN AND ANTITHROMBIN

Protease-activated receptors (PARs) form the molecular link between coagulation and inflammation. PAR1 in particular is implicated in sepsis [22], and while it exerts cytoprotective effects when stimulated by activated protein C (APC) or low-dose thrombin, it exerts disruptive effects on endothelial-cell barrier function when activated by high-dose thrombin. APC cleaves PAR1 when it is associated with either the endothelial protein C receptor (EPCR) or CD11b/ /CD18, which results in broad cytoprotective effects mediated by sphingosine 1 phosphate (S1P) receptor 1 (S1P1). APC associated with EPCR cleaves PAR-1 initiating cell signalling with cytoprotective effects that includes anti-inflammatory, anti-apoptotic activities and altered gene expression [9]. Activation of PAR1 by high dose thrombin results in barrier disruptive effects in endothelial cells via an S1P3 dependent mechanism. Thrombus formation results in reduced tissue oxygenation impaired by the loss of endothelial barrier function and a disturbed balance between S1P1 and S1P3 within the vascular wall. This is in part due to induction of S1P3 through PAR1 as a result of a reduced ratio of APC to thrombin [22]. PC is activated by the thrombin–thrombomodulin complex on the endothelial surface, and this activation is facilitated by EPCR. APC exerts its anticoagulant activities through the proteolytic inactivation of factors Va and VIIIa aided by protein S on negatively charged phospholipid membranes. The mechanisms responsible for the decrease in AT and PC activity in sepsis are thought to be their consumption during activated coagulation, impaired synthesis in the liver, degradation by neutrophil elastase and other enzymes, and leakage from the endovascular space.

The capacity to generate activated protein C is impaired in part by reduced expression of thrombomodulin (TM) and the EPCR. Thrombomodulin (CD141) is an transmembrane glycoprotein which by binding thrombin, prevents fibrinogen conversion to fibrin and prevents thrombin from interacting with platelets [23]. Thrombomodulin accelerates the thrombin-catalyzed conversion of protein C to APC, which suppresses the release of TNF-α and IL-1β. TM binds to HMGB1 preventing its interaction with RAGE-products and supports the proteolytic cleavage of HMGB1 by thrombin. A novel biological agent, rhsTM (recombinant human soluble thrombomodulin), exhibits anti-inflammatory, anticoagulant, antifibrinolytic properties. RhsTM binds to histones and neutralizes the prothrombotic action of histones providing a mechanism for its effectiveness in DIC [24]. A multicenter, double-blind, randomized trial performed in order to evaluate the efficacy and safety of rhsTM (ART-123) for the DIC treatment, revealed that rhsTM therapy is more effective and safer than low-dose heparin. In a study of 86 patients with sepsis-induced DIC, lower mortality and improved SOFA scores were associated with an infusion of rTM (recombinant thrombomodulin) versus those not treated with rTM (37% vs. 58%, $P = 0.038$) [25]. According to the newest data, Japan, during the 2010–2012 period, significantly increased the use of rhs-TM and decreased the use of AT, heparin and protease inhibitors in the treatment of sepsis-induced DIC [26].

AT is a single-stranded glycoprotein which is synthesized in the liver and inhibits the activity of thrombin and activated factors VII, IX, X, XI and XII. Antithrombin forms a 1:1 complex with thrombin, inactivating its enzymatic activity. Iba *et al.* [27] reported the results of a non-randomized, multi-institutional, post-marketing survey performed in order to determine the optimal AT dose for septic DIC treatment. In the above-described survey, 307 septic patients having an AT activity less than 40% and who had undergone AT substitution at a dose 1,500 IU per day, or 3,000 IU per day for 3 consecutive days, were analyzed. DIC was defined according to the Japanese Association for Acute Medicine DIC (JAAM DIC) criteria [27]. The scoring system included the SIRS score, platelet count, fibrin/fibrinogen degradation product (FDP), or D-dimer and prothrombin time ratio. They reported survival rates of 65.2% in patients receiving 1,500 IU per day of AT and 74.7% in patients receiving 3,000 IU per day. A logistic regression analysis showed that the higher dose (3,000 IU per day) was associated with a better 28-day survival outcome without increasing the risk of bleeding in DIC patients [28].

THE ROLE OF GLYCOCALYX AND ENDOTHELIUM

Intact endothelium functions as an antithrombotic surface preventing inappropriate activation of coagulation. Endothelial cells regulate haemostatic balance by the site-specific release of pro- and anticoagulant factors. As the PC system and TFPI are connected to the endothelium, ECs maintain their anticoagulant function. ECs are the main producer of proinflammatory, procoagulant and antifibrinolytic factors, as well as of those with the opposite actions- anti-inflammatory anticoagulant, and profibrinolytic properties. ECs synthesize von Willebrand factor, protease-activated receptors (PARs), express prostacyclin , nitric oxide, TFPI, heparin sulfate, thrombomodulin, as well as EPCR. Once activated or injured, ECs secrete into the local environment mostly procoagulant or antifibrinolytic components, such as von Willebrand factor (vWF), thromboxane A2 (TXA2) or PAI-1.The expression or secretion of components with anticoagulant and profibrinolytic properties is significantly reduced [26].

Glycocalyx and EC damage are associated with consequences like capillary leakage, inflammation with platelet activation, and microvascular thrombus formation [29].

SEPTIC DISTURBANCES IN PLATELETS COUNT AND FUNCTION

The function of the platelets goes beyond haemostatic regulation, and platelets are key mediators of the immuno-inflammatory response to infection. Platelets can be activated by PAF and thrombin. Thrombin is an important platelet agonist via PAR1, PAR3 and PAR4, which are present on the platelet membrane [30]. Platelets after activation with thrombin are able to express more than 300 proteins (coagulation factors, chemokines, mitogenic factors, adhesive proteins) which undergo different patterns of release during their activation [30]. Platelets, by expressing selectin on their surface and/or by releasing soluble P-selectin, enhance the expression of TF on monocytes. The engagement of neutrophil TREM-1, for which platelets express a ligand, results in increased release of cytokines and chemokines. Endothelial cells are activated by platelet derived CD40L (ligand) and platelet derived IL1β-positive microparticles, after which ECs secrete adhesion molecules and TF [30]. Activated platelets amplify thrombin generation by providing the anionic phospholipid surface onto which coagulation occurs. Sepsis-induced platelet activation results in the release of triggering a receptor expressed on myeloid cells-like (TREM-like) transcript-1 (sTLT-1).TLT-1 is a receptor expressed only on platelet and megakaryocyte lineage and moved to the platelet surface after activation with thrombin, LPS and collagen. TLT-1 seems to be a regulator of haemostasis during sepsis via autocrine stimulation of increased platelet aggregation [31]. Platelets may exert direct cytotoxic effects by releasing of granzyme B and cationic antimicrobial proteins while platelet derived microparticules may be cytotoxic as a result of containing superoxide.

Thrombocytopenia is a known risk factor for death and complications in sepsis and is included in severity scores that have been validated in sepsis, such as the Sequential Organ Failure Assessment (SOFA) [32]. Thrombocytopenia in sepsis occurs as part of DIC, as a result of impaired production due to inflammatory mediators, increased platelet consumption, or destruction due to the ongoing generation of fibrin, and mostly as a combination of these. A drop in a platelet count of 30% and more is an independent death predictor.

Measuring immature platelet fractions (IPF%) allows one to differentiate between thrombocytopenia caused by increased platelet destruction and bone marrow failure. Increased IPF% is related to thrombotic events including DIC in sepsis [30].

In research by Gafter-Gvili *et al.* [33] concerning a 1052 patient cohort with Staphylococcus bacteremia, thrombocytopenia was defined as a platelet count less than 150 G L^{-1} and was present at the onset of sepsis in 235 patients (22.3%). The primary outcome was 30-day all-cause mortality which was accelerated and significantly higher among patients with thrombocytopenia (unadjusted OR: 2.44; 95% CI: 1.82–3.28; $P < 0.001$). Higher and accelerated mortality was associated with the degree of thrombocytopenia: death occurred in 23 (76.7%) of 30 patients with platelet counts of < 50 G L^{-1} ; in 47 (62.7%) of 75 patients with platelet counts of 50–99 G L^{-1} ; in 62 (47.7%) of 130 patients with platelet counts of 100–149 G L^{-1} ; in 238 (35.1%) of 678 patients with platelet counts of 150–400 G L^{-1} [33].

The activated platelets undergo a shape change from disc-shaped cells into spherical-shaped cells, upregulate the expression of receptors like P-selectin, degranulate and aggregate promoting their own adhesion with the endothelium, other platelets and leucocytes, leading to the production of NETs [34]. In a study by Reddi *et al.* [35], it was revealed that poor platelet aggregation responses were associated with high SOFA and APACHE II scores. Amongst patients with septic shock, the aggregation response to both ADP (adenosine diphosphate) and arachidonic acid was inversely correlated with their SOFA score (n = 26, r = – 0.51 and –0.36, respectively, $P < 0.05$). The aggregation of platelets from septic shock patients was also inversely correlated with their APACHE II score (n = 26, r = –0.44 and –0.47 respectively, $P < 0.05$) (35).

Davies *et al.* [36] showed reduced platelet aggregometry measurements in patients with severe sepsis and septic shock when compared to SIRS and uncomplicated sepsis. Platelet aggregation is enhanced in the presence of lipopolysaccharide (LPS) *in vitro*, in blood, endotoxin directly binds to CD14 receptor on monocytes and binds to ECs after com-

plexing with lipopolysaccharide binding protein (LBP) and TLR-4. In endotoxin-induced inflammatory settings, platelets can be directly activated by proinflammatory cytokines or PAF. The activation of P2Y12 receptor, a chemoreceptor for ADP, is essential for ADP-mediated complete activation of glycoprotein (GP) IIb/IIIa and Ia/IIa. After platelets activation fibrinogen binds to multiple GPIIb/IIIa receptors, bridging platelets and facilitating platelet aggregation.

Recently, the role of platelets in sepsis-associated endothelial dysfunction has been reported. The data indicate that anti-platelet drugs could modulate the development of organ failure in sepsis, not only by an inhibition of the haemostatic function of platelets but also by an inhibition of their interaction with ECs [37]. Acetylsalicylic acid (ASA) suppress the production of prostaglandins and thromboxanes, and stimulates the synthesis of 15-epi-lipoxin A4, which increases the synthesis of nitric oxide, inhibiting the interactions between leukocytes and ECs. In a general population of ICU admissions, those on antiplatelet therapy have a decreased mortality [38] and have a decreased risk of developing multi-organ failure [39]. In ICU patients with septic shock treated with antiplatelet therapy, a reduction in mortality was observed [34].

THERAPEUTIC OPTIONS FOR SEPTIC COAGULOPATHY

Despite developments in the pathophysiology of sepsis, there is no specific pharmacotherapy for septic coagulopathy [40] while the main factor of septic coagulopathy treatment is the management of sepsis/septic shock. Surviving Sepsis Campaign Guidelines and the Guidelines for Prevention of Venous Thromboembolism in Nonsurgical Patients have recommended thromboprophylaxis with UFH or LMWH for septic patients [2, 41]. Wang *et al.* [42] in a meta-analysis assessed the effects of heparin on short-term mortality in adult patients with sepsis and severe sepsis. Nine publications were included in the meta-analysis. According to its results, heparin decreased 28-day mortality (n = 3,482, OR = 0.656, 95% CI: 0.562–0.765, $P < 0.0001$) in patients with severe sepsis while heparin had no effect on bleeding events in sepsis (7 RCTs, n = 2,726; OR = = 1.063; 95% CI: 0.834–1.355; $P = 0.623$; and $I^2 = 20.9$). In their conclusions, the authors stated that the use of heparin for sepsis is safe with no increase in the risk of bleeding [42]. Zarychanski *et al.* [43], in systemic review and meta-analysis, evaluated the efficacy and safety of heparin in patients with sepsis, septic shock and DIC associated with infection. Nine trials enrolling 2,637 patients were included. According to these results, the authors stated that although heparin in patients with sepsis, septic shock and DIC associated with infection may be associated with decreased mortality, the overall impact remains uncertain [43]. In HETRASE study results (A Randomized Clinical Trial of Unfractioned Heparin for the Treatment of Sepsis) the efficacy of UFH for sepsis was denied [44].

Thrombomodulin is an anticoagulant converting thrombin into an APC generator. PAMPs, DAMPs and complements are sequestrated by lectin-like domain of rhsTM and these are APC-independent activities of rhsTM [45]. As the expression of thrombomodulin is downregulated during septic DIC, substitution with recombinant human soluble TM is a therapeutic option for the management of sepsis with coagulopathy [24]. RhsTM was approved in Japan for DIC treatment in 2008 [46]. An international phase III clinical trial evaluating the efficacy of TM in patients with severe sepsis and coagulopathy is ongoing in the USA, South America, Asia, Australia, the European Union, and other countries (https://clinicaltrials.gov/ct2/show/NCT01598831?term=ART-123&rank=2).

Wiedermann *et al.* [47] demonstrated the potential efficacy of antithrombin for septic DIC while an RCT conducted by the JAAM/DIC Study Group demonstrated that antithrombin treatment resulted in significantly decreased DIC scores and better recovery rates from DIC compared with those observed in the control group (no AT treatment) on day 3. The incidence of minor bleeding complications did not increase, and no major bleeding related to AT treatment was observed. Although the platelet count significantly increased, AT did not influence the SOFA score or markers of coagulation and fibrinolysis on day 3 [48] According to the authors, the moderate dose of AT — 30 IU kg^{-1} day^{-1} increases the DIC recovery rate without any risk of bleeding in patients with septic DIC. A study by Iba *et al.* [49], published in 2016, presented results from a group of 159 patients with septic DIC with AT ≤ 70% who had undergone AT supplementation. The 28-day mortality in the study group was 27%. Survivors exhibited a higher peak AT activity than non-survivors (85.1% vs. 65.0%, $P = 0.027$). Bleeding events were observed in 4.13% (major bleeding: 1.65%) of the patients, and the coadministration of rTM did not increase the risk of bleeding (with rTM: 4.11% vs. without rTM: 4.17%). Heparin was concomitantly used in 22 (18.2%) cases, while its use non-significantly increased the bleeding risk (with heparins: 9.09% vs. without heparins: 3.03%; $P = 0.224$) [49].

Since there is a significant heterogeneity regarding septic patients, in the treatment for septic DIC the proper choice of drug, timing and matched dose depend strictly on the patient's coagulation results and clinical condition.

CONCLUSIONS

The host's defence to infectious invasion is a highly regulated process involving inflammatory and anti-inflammatory components. The important features in sepsis which contribute to the outcome are the activation of coagulation and

downregulation of anticoagulation and fibrinolysis. Each targeted treatment for sepsis should restore the balance of haemostasis and should be tailored to preserve the function of the host's defence mechanisms. A revised understanding of the molecular mechanisms responsible for the bidirectional interaction between inflammation and hemostasis in sepsis may be helpful in revealing new therapeutic options concerning septic patients and creates the possibility for the reduction of mortality in sepsis.

ACKNOWLEDGEMENTS

1. Source of funding: none.
2. Conflict of interest: none.

References:

1. *Tsalik EL, Jaggers LB, Glickman SW et al.:* Discriminative value of inflammatory biomarkers for suspected sepsis. J Emerg Med 2012; 43: 97–106. doi: 10.1016/j.jemermed.2011.05.072
2. *Singer M, Deutschman CS, Seymour CW et al.:* The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801–810 doi.10.1001/jama.2016.0287
3. *Engelmann B, Massberg S:* Thrombosis as an intravascular effector of innate immunity. Nat Rev Immunol 2013; 13: 34–45. doi: 10.1038/nri3345.
4. *Semeraro N, Ammolo CT, Semeraro F, Colucci M:* Coagulopathy of acute sepsis. Semin Thromb Hemost 2015; 41: 650–658. doi: 10.1055/s-0035-1556730.
5. *Simmons J, Pittet JF:* The Coagulopathy of Acute Sepsis. Curr Opin Anaesthesiol 2015; 28: 227–236.doi.10.1097/ACO0000000000000163.
6. *Gould TJ, Lysov Z, Liaw PC:* Extracellular DNA and histones: double-edged swords in immunothrombosis. J Thromb Haemost 2015; 13 (Suppl. 1): S82–S91. doi: 10.1111/jth.12977.
7. *Allen KS, Sawheny E, Kinasewitz GT:* Anticoagulant modulation of inflammation in severe sepsis. World J Crit Care Med 2015; 4: 105–115. doi: 10.5492/wjccm.v4.i2.105.
8. *Okamoto K, Tamura T, Sawatsubashi Y:* Sepsis and disseminated intravascular coagulation. J Intensive Care 2016; 4: 23.doi:10.1186/s40560-016-0149-0.
9. *van der Poll. Herwald H:* The coagulation system and its function in early immune defense. Thromb Haemost 2014; 112: 640–648. dx.doi.org/10.1160/TH14-01-0053.
10. *MacDonald B, Urrutia R, Yipp BG, Jenne CN, Kubes P:* Intravascular neutrophil extracellular traps capture bacteria from the bloodstream during sepsis. Cell Host Microbe 2012; 12: 324–333. doi.10.1016/j.chom.2012.06.011.
11. *Petros S, Kliem P, Siegemund T. Siegemund R:* Thrombin generation in severe sepsis. Thromb Res 2012; 129: 797–800. doi: 10.1016/j.thromres.2011.08.004.
12. *Daudel F, Kessler U, Folly H, Lienert JS, Takala J, Jakob SM:* Thromboelastometry for the assessment of coagulation abnormalities in early and established adult sepsis: a prospective cohort study. Crit Care 2009; 13: R42. doi: 10.1186/cc7765.
13. *Muller MC, Meijers JC, Vroom MB, Juffermans NP:* Utility of thromboelastography and/or thromboelastometry in adults with sepsis: a systematic review. Crit Care 2014; 18: R30. doi:10.1186/cc13721.
14. *Adamzik M, Langemeier T, Frey U et al.:* Comparison of thrombelastometry with Simplified Acute Physiology Score II and Sequential Organ Failure Assessment scores for the prediction of 30-day survival: a cohort study. Shock 2011; 35: 339–342. doi: 10.1097/SHK.0b013e318204bff6.
15. *Levi M, Opal SM:* Coagulation abnormalities in critically ill patients. Crit Care 2006;10: 222. doi:10.1186/cc4975.
16. *Fiusa MML, Carvalho-Filho A, Annichino-Bizzacchi JM, De Paula EV:* Causes and consequences of coagulation activation in sepsis: an evolutionary medicine perspective. BMC Med 2015; 13: 105. doi: 10.1186/s12916-015-0327-2.
17. *Angus DC, van der Poll T:* Severe sepsis and septic shock. N Engl J Med 2013; 369: 840–851. doi: 10.1056/NEJMra1208623.
18. *Savioli M, Cugno M, Polli F et al.:* Tight glycemic control may favor fibrinolysis in patients with sepsis. Crit Care Med 2009; 37: 424–431.
19. *Gando S:* Role of fibrinolysis in sepsis. Semin Thromb Hemost. 2013; 39: 392–399. doi: 10.1055/s-0033-1334140.
20. *Lorente L, Martín MM, Borreguero-León JM et al.:* Sustained high plasma plasminogen activator inhibitor-1 levels are associated with severity and mortality in septic patients. Thromb Res. 2014; 134: 182–186.
21. *Koyama K, Madoiwa S, Nunomija S et al.:* Combination of thrombin-antithrombin complex, plasminogen activator inhibitor-1, and protein C activity for early identification of severe coagulopathy in initial phase of sepsis: a prospective observational study. Crit Care 2014; 18: R13. doi.10.1186/cc13190.
22. *Levi M, van der Poll T:* Inflammation and coagulation. Crit Care Med 2010; 38 (Suppl): S26–S34. doi: 10.1097/CCM.0b013e3181c98d21.
23. *Levi M, Van Der Poll T:* Thrombomodulin in sepsis. Minerva Anestesiol 2013; 79: 294–298.
24. *Ogawa Y, Yamakawa K, Ogura H et al.:* Recombinant human soluble thrombomodulin improves mortality and respiratory dysfunction in patients with severe sepsis. J Trauma Acute Care Surg 2012; 72: 1150–1157. doi: 10.1097/TA.0b013e3182516ab5.
25. *Vincent JL, Ramesh MK, Ernest D et al.:* Diagnosis and treatment of disseminated intravascular coagulation (DIC) according to four DIC guidelines. A randomized, double-blind, placebo controlled, phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. Crit Care Med 2013; 41: 2069–2079. doi: 10.1097/CCM.0b013e31828e9b03.
26. *Murata A, Okamoto K, Mayumi T, Muramatsu K, Matsuda S:* Recent change in treatment of disseminated intravascular coagulation in Japan: an epidemiological study based on a national administrative database. Clin Appl Thromb Hemost 2016; 22: 21–27. doi: 10.1177/1076029615575072.
27. *Gando S, Saitoh D, Ogura H et al.:* Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) study group: Natural history of disseminated intravascular coagulation diagnosed based on the newly established diagnostic criteria for critically ill patients: results of a multicenter, prospective survey. Crit Care Med 2008; 36: 145–150.
28. *Iba T, Saito D, Wada H, Asakura H:* Efficacy and bleeding risk of antithrombin supplementation in septic disseminated intravascular coagulation: a prospective multicenter survey. Thromb Res 2012; 130: e129–e133. doi: 10.1016/j.thromres.2012.03.021.
29. *Ostrowski SR, Haase N, Müller RB et al.:* Association between biomarkers of endothelial injury and hypocoagulability in patients with severe sepsis: a prospective study. Crit Care 2015; 19: 191. doi: 10.1186/s13054-015-0918-5.
30. *de Stoppelaar SF, van't Veer C, van der Poll T:* The role of platelets in sepsis. Thromb Haemost 2014; 112: 666–677.doi.10.1160/TH14-02-0126.
31. *Washington AV, Gibot S, Acevedo I et al.:* TREM-like transcript-1 protects again inflammation-associated haemorrhage by facilitating platelet aggregation in mice and humans. J Clin Invest 2009; 119: 1489–1501. doi: 10.1172/JCI36175.
32. *Vincent JL, Moreno R, Takala J et al.:* The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996; 22: 707–710.
33. *Gafter-Gvili A, Mansur N, Bivas A et al.:* Thrombocytopenia in Staphylococcus bacteremia: risk factors and prognostic importance. Mayo Clin Proc 2011; 86: 389–396. doi:10.4065/mcp.2010.0705.
34. *Toner P, McAuley DF, Shyamsundar M:* Aspirin as a potential treatment in sepsis or acute respiratory distress syndrome. Crit Care 2015; 19: 374. doi: 10.1186/s13054-015-1091-6.
35. *Reddi B, Ianella SM, O'Connor S, Deane A, Willoughby S, Wilson D:* Attenuated platelet aggregation in patients with septic shock is independent from the activity state of myosin light chain phosphorylation or a reduction in Rho kinase-dependent inhibition of myosin light chain phosphatase. Intensive Care Med Exp 2015; 3: 37. doi: 10.1186/s40635-014-0037-7.
36. *Davies GR, Mills G, Lawrence M et al.:* The role of whole blood impedance aggregometry and its utilisation in the diagnosis and prognosis of patients with systemic inflammatory response syndrome and sepsis in acute critical illness. PLoS One. 2014; 9: e108589. doi:10.1371/journal.pone.0108589.
37. *Winning J, Reichel J, Eisenhut Y et al.:* Anti-platelet drugs and outcome in severe infection: Clinical impact and underlying mechanisms Platelets 2009; 20: 50–57. doi: 10.1080/09537100802503368.

38. *Tsai MJ, Ou SM, Shih CJ et al.:* Association of prior anti-platelet agents with mortality in sepsis patients: a nationwide population-based cohort study. Intensive Care Med 2015; 41: 806–813. doi: 10.1007/s00134-015-3760-y.
39. *Lösche W, Boettel J, Kabisch B, Winning J, Claus RA, Bauer M:* Do aspirin and other antiplatelet drugs reduce the mortality in critically ill patients? Thrombosis 2012; 2012: 720254. doi: 10.1155/2012/720254.
40. *Martin-Loeches I, Levy MM, Artigas A:* Management of severe sepsis: advances, challenges, and current status. Drug Des Devel Ther 2015; 9: 2079–2088. doi: 10.2147/DDDT.S78757.
41. *van Roessel S, van der Laan A, de Pont AC:* What is the best heparin to treat sepsis with? Crit Care Med 2015; 43: e 212–213. doi: 10.1097/CCM.0000000000000916.
42. *Wang Ch, Chunjie Ch, Lei G et al.:* Heparin therapy reduces 28-day mortality in adult severe sepsis patients: a systemic review and meta-analysis. Critical Care 2014; 18: 563. doi: 10.1186/s13054-014-0563-4.
43. *Zarychanski R, Abou-Setta AM, Kanji S et al.:* The efficacy and safety of heparin in patients with sepsis: a systemic review and meta-analysis. Crit Care Med 2015; 43: 511–518. doi: 10.1097/CCM0000000000000763.
44. *Jaimes F, de la Rosa G, Morales C et al.:* Unfractioned heparin for treatment of sepsis: a randomized clinical trial (The HETRASE study). Crit Care Med 2009; 37: 1185–1196. doi: 10.1097/CCM.0b013e31819c06bc
45. *Ito T:* DAMPs and DAMPs as triggers for DIC. J Intensive Care 2014; 2: 67. doi:10.1186/s40560-014-0065-0.
46. *Yamakawa K, Ogura H, Fujimi S et al.:* Recombinant human soluble thrombomodulin in sepsis-induced disseminated intravascular coagulation: a multicenter propensity score analysis. Intensive Care Med 2013; 39: 644–652. doi: 10.1007/s00134-013-2822-2.
47. *Wiedermann CJ, Kaneider NC:* A systematic review of antithrombin concentrate use in patients with disseminated intravascular coagulation of severe sepsis. Blood Coagul Fibrinolysis 2006; 17: 521–526. doi:10.1097/01.mbc.0000245302.18010.40.
48. *Gando S, Saitoh D, Ishikura H et al.:* Japanese Association for Acute Medicine Disseminated Intravascular Coagulation (JAAM DIC) Study Group for the JAAM DIC Antithrombin Trial (JAAMDICAT). A randomized, controlled, multicenter trial of the effects of antithrombin on disseminated intravascular coagulation in patients with sepsis. Crit Care. 2013; 17: R297 doi: 10.1186/cc13163.
49. *Iba T, Gando S, Saitoh D et al.:* Efficacy and bleeding risk of antithrombin supplementation in patients with septic disseminated intravascular coagulation. A third survey. Clin Appl Thromb Hemost 2016. doi:10.1177/1076029616648405.

Corresponding author:
Małgorzata Lipińska-Gediga, MD
4th Military Hospital of Wroclaw
Department of Anaesthesiology and Intensive Care
Weigla 5, 50–981 Wrocław, Poland
e-mail: starling@poczta.onet.pl

Received: 10.09.2016
Accepted: 2.11.2016