Review Article

Coagulopathy of sepsis

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Summary

Disseminated intravascular coagulation (DIC) is a common phenomenon in patients with sepsis, but the clinical implications of this condition are not clear. Clinical trials with coagulation inhibitors have failed to show a significant benefit concerning survival. DIC is primarily a laboratory diagnosis, based on the combination of elevated fibrin-related markers (FRM), with decreased procoagulant factors and platelets. Non-overt DIC is observed in most patients with sepsis, whereas overt DIC is less frequent. Patients with overt DIC may display consumption coagulopathy and purpura fulminans. Consumption coagulopathy is a bleeding disorder caused by low levels of platelets and procoagulant factors associated with massive coagulation activation. Purpura fulminans is caused by widespread microvascular thrombosis, resulting in tissue necrosis. Treatment with drotrecogin alfa (activated) improves survival and other outcome parameters in severe sepsis, including a subgroup of patients fulfilling the laboratory criteria of overt DIC. No randomized trials demonstrating effective therapies in consumption coagulopathy have been published. Bleeding patients with consumption coagulopathy are most frequently treated with platelet transfusions and various plasma products including fresh frozen plasma and coagulation factor concentrates. Based on case reports, treatment with drotrecogin alfa (activated) or substitution of protein C have been recommended for adjuvant treatment of sepsis-related purpura fulminans.

Coagulation activation in sepsis

Sepsis is defined as a systemic inflammatory response syndrome occurring during infection (1). Activation of blood coagulation is a common observation in patients with sepsis (2, 3). Nearly all patients with severe sepsis according to the American College of Chest Physicians (ACCP) criteria (1) display elevated levels of activation products of blood coagulation (4). Since in most cases, no single localized clot is detected, the source of activation products is non-localized or disseminated. Coagulation activation may occur in the flowing blood, on the endothelial surface, at endothelial lesions, in the perivascular tissue, and in areas not directly linked to the vascular bed, and may or may not be associated with the formation of particulate clots.

Tissue factor production is upregulated in activated monocytes (5) and neutrophils (6) in response to endotoxin, bacterial peptidoglycans (7), or other substances (8), activating coagulation in the flowing blood (Fig. 1). Tissue factor (TF) production is regulated by nuclear factor kappa B (NFκB) (9). TF is also stored in the α-granules and the open canalicular system of resting platelets, and is exposed on the cell surface after platelet
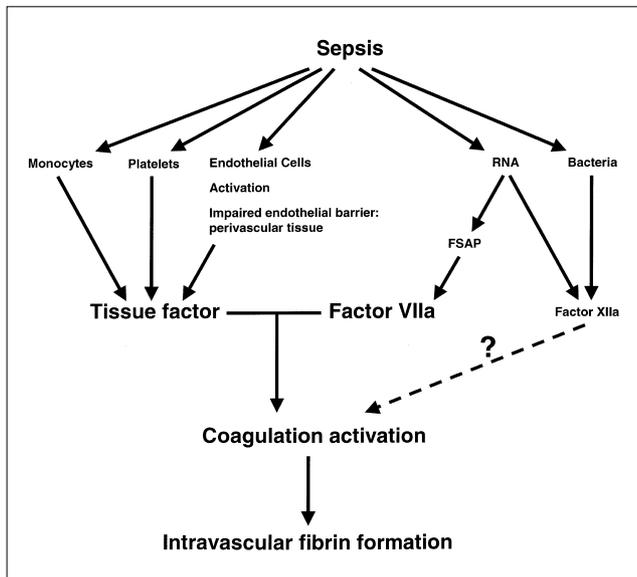
Figure 1: Coagulation activation process in sepsis.

activation and shedding of platelet microvesicles (10). Endothelial cells may bind inflammatory cells via various adhesion molecules, again leading to activation of coagulation (11).

Apoptosis of endothelial cells (12, 13) and other cell types causes exposure of procoagulant phospholipid compounds. Released intracellular compounds such as RNA may activate coagulation via the activation of the intrinsic system (Preissner KT, personal communication) or by activation of the factor VII-activating protease (FSAP) (14, 15). Several investigators have demonstrated activation of factor XII and other components of the intrinsic system in sepsis (16, 17). Activation of the intrinsic system may also take place on the surface of bacteria (18, 19). The role of this process for the generation of thrombin remains unclear, since antibodies against factor XII were not able to prevent intravascular fibrin formation in a baboon model of *E.coli* sepsis (20). The perivascular tissue contains tissue factor-bearing cell types, alongside with other coagulation activation-promoting agents such as collagens. An increase in permeability caused by an impaired endothelial barrier leads to leakage of plasma components into the perivascular space (21, 22), bringing coagulation factors in contact with the procoagulant components of the perivascular tissue.

Although coagulation activation in sepsis is initiated by tissue factor-dependent mechanisms, the procoagulant response is dependent upon the feedback loop of coagulation activation (23, 24). Activated protein C is generated in the course of coagulation activation (25) and influences this system by inhibiting factors Va and VIIIa (26).

Coagulation activation leads to the activation of prothrombin. Thrombin cleaves fibrinopeptides A from fibrinogen. The resulting desAA-fibrin monomers rapidly polymerize with other fibrin monomers, with fibrinogen, or with proteolytic

fragments of fibrinogen and fibrin. Soluble fibrin complexes are cofactors in thrombin-induced factor XIII activation and in tPA-induced plasminogen activation. Factor XIIIa, but also non-activted 'proenzyme' factor XIII (27, 28) induce the formation of covalent bonds between fibrin monomer units within the fibrin complex. Due to a variable degree of factor XIII-induced fibrin crosslinking, and proteolytic cleavage by plasmin and other proteases such as granulocyte elastase, fibrin complexes and fibrin derivatives in patients with sepsis are heterogeneous.

Fibrin formation may occur in the flowing blood or localized at endothelial lesions or in the perivascular tissue. Assays for D-dimer antigen do not distinguish between fibrin complexes containing dimerized D-domains, and proteolytic fragments of crosslinked fibrin and do not distinguish between fibrin derivatives formed in flowing blood and fibrin derivatives released from particulate clots.

Natural anticoagulants such as antithrombin and protein C are depressed in sepsis (29). Antithrombin reacts as negative acute phase protein (30). Impaired liver function in sepsis leads to decreased protein synthesis and consequently a reduced production of hepatic coagulation factors and inhibitors. Reduced levels of antithrombin and protein C may also be caused by protein loss into the extravasal space, or coagulation activation-dependent consumption (31).

Non-overt DIC in sepsis

Non-overt DIC (32, 33) is defined as a condition of disseminated coagulation activation without clinical signs of bleeding or thrombosis. There is no conclusive evidence in humans that this 'latent coagulation' (34) in sepsis is actually part of the pathogenetic process leading to organ dysfunction or death. There is also no proof that it is an uncontrolled process or indicates decompensation of coagulation and fibrinolytic systems. The factors leading to a possible transition of non-overt DIC to overt DIC have not been identified. In general intensive care patients, the non-overt DIC score system proposed by the DIC subcommittee of the International Society for Thrombosis and Haemostasis (ISTH) (35) identified patients with increased mortality, but did not predict overt DIC (Toh CH, presentation at DIC subcommittee meeting at the ISTH congress in Birmingham, U.K., July 12th, 2003).

Alternatively, 'latent coagulation' in sepsis may be interpreted as part of the defense mechanisms of the vascular system (36). Fibrin binds active thrombin, thereby modulating *in vivo* thrombin activity (37). Fibrin is necessary for effective activation of plasminogen by tissue plasminogen activator (tPA) (38-40). In patients treated with thrombin-like snake venom enzymes such as ancrod, the presence of intravascular fibrin induces a massive profibrinolytic response, leading to intravascular fibrinogen degradation by plasmin (27, 41). In sepsis, high levels of activation products of blood coagulation and, specifi-

Table 1: Definitions of procoagulant conditions observed in sepsis.

Overt DIC	Consumption Coagulopathy	Defibrination Syndrome	Purpura fulminans
- Clinical condition which may be associated with DIC - Elevated levels of FRM - PT prolongation / Increased INR - Decreased platelet count - Decreased levels of antithrombin and protein C - (Decreased fibrinogen level)	- Laboratory criteria of overt DIC - Bleeding (wounds, puncture sites, mucous membranes, other locations)	- Presence of enzymatic activity of thrombin or thrombin-like enzymes - Elevated levels of Plasmin-antiplasmin complexes (PAP) or other indicators of plasmin generation - Elevated levels of FRM - Low fibrinogen level - Bleeding (wounds, puncture sites, mucous membranes, other locations)	- Bacterial or viral infection which may be associated with development of purpura fulminans (meningococcal or pneumococcal infections, Haemophilus, others) - Elevated levels of FRM - Low protein C levels - Microvascular thrombosis (skin, organs) - Tissue necrosis - Bleeding

cally, soluble fibrin complexes may indicate a high level of defense rather than a sign of decompensation (34).

Plasminogen activator inhibitor 1 (PAI-1) levels are often elevated in patients with sepsis (42), leading to reduced levels of tPA available for plasminogen activation despite elevated total plasma levels of tPA (43, 44). High levels of PAI-1 predict adverse outcome in severe sepsis (45). Genetic polymorphisms associated with elevated PAI-1 levels result in reduced survival in sepsis and other conditions associated with DIC (46, 47). Although most patients with sepsis, severe sepsis and septic shock display some activation of fibrinolysis (44), high plasma fibrinogen levels, despite massively elevated fibrin derivatives, indicate an imbalance between fibrin formation and fibrin degradation, potentially leading to microvascular occlusion. According to a recent study, high, rather than low plasma fibrinogen levels are associated with poor clinical outcome in DIC (48).

Sepsis-related organ dysfunction has been attributed to microvascular thrombosis (49). Animal experiments in baboons have shown fibrin deposition in the kidneys in response to infusion of high doses of live *E.coli* bacteria after priming of the immune system with an infusion of killed *E.coli*. Renal failure was prevented by infusion of active site inhibited factor VIIa (factor VIIai) before administration of the live bacteria (50). No fibrin thrombi in the microvasculature of any organ were found in animal models of hyperdynamic sepsis (51). Skjorten et al. detected microthrombi in blood vessels of various organs, including liver, lung, kidney, skin, adrenals, and heart in 100 autopsied cases of clinically suspected DIC (52). In a series of 4906 necropsies, Tanaka and Imamura found histological evidence of microvascular thrombi in 319 patients (53). Watanabe et al. detected microthrombi in two or more organs in 51/1729 patients (54). So far, no studies have systematically analyzed the relation between post-mortem evidence of microvascular thrombi and the pre-mortem diagnosis of DIC. Recent investigations based on necropsy studies in humans indicate that organ dysfunction is an effect of cell hibernation or stunning rather than thrombosis- and ischemia-induced cell necrosis (13).

Overt DIC in sepsis

Overt DIC is defined by the combination of a clinical condition, which may be associated with disseminated intravascular coagulation activation, with various laboratory criteria (Table 1). In a recent study, overt DIC, according to the laboratory criteria of the DIC subcommittee of the ISTH, was present in 22% of patients with severe sepsis (55). Although it has been shown that overt DIC has a predictive value concerning clinical outcome (56, 57), general recommendations for treatment cannot be made on the basis of this laboratory diagnosis. It must be emphasized that most authors define overt DIC on the basis of laboratory criteria (3, 35, 56, 58), in combination with underlying diseases. With this definition, overt DIC is not associated with any specific clinical symptoms. Consequently, there is no specific therapy for overt DIC.

Two diagnoses that are synonymous to overt DIC in sepsis are often used: consumption coagulopathy and purpura fulminans (Fig. 2). Consumption coagulopathy is an acquired bleeding disorder observed in patients with sepsis as well as in a variety of other diagnoses, ascribed to the consumption of procoagulant factors in the course of coagulation activation. The coagulation process may be localized such as in vascular malformations or aneurysms or non-localized as in sepsis or disseminated malignant disease. Bleeding occurs from venipuncture sites, tissue lesions, mucous membranes, or from the gastrointestinal, or genitourinary tract. In contrast to purpura fulminans, massive cutaneous bleeding is rare. A specific type of consumption coagulopathy is the defibrination syndrome (59), characterized by the combination of very low plasma fibrinogen levels, with high levels of fibrin degradation products as well as fibrinogen degradation products in plasma. Clinical and laboratory criteria for overt DIC, consumption coagulopathy, defibrination syndrome, and sepsis-associated purpura fulminans are shown in table 1.

Purpura fulminans is found in the context of meningococcal (60) pneumococcal (61), and other bacterial or viral infections (62-64). Fibrin deposits can be detected in the microvasculature
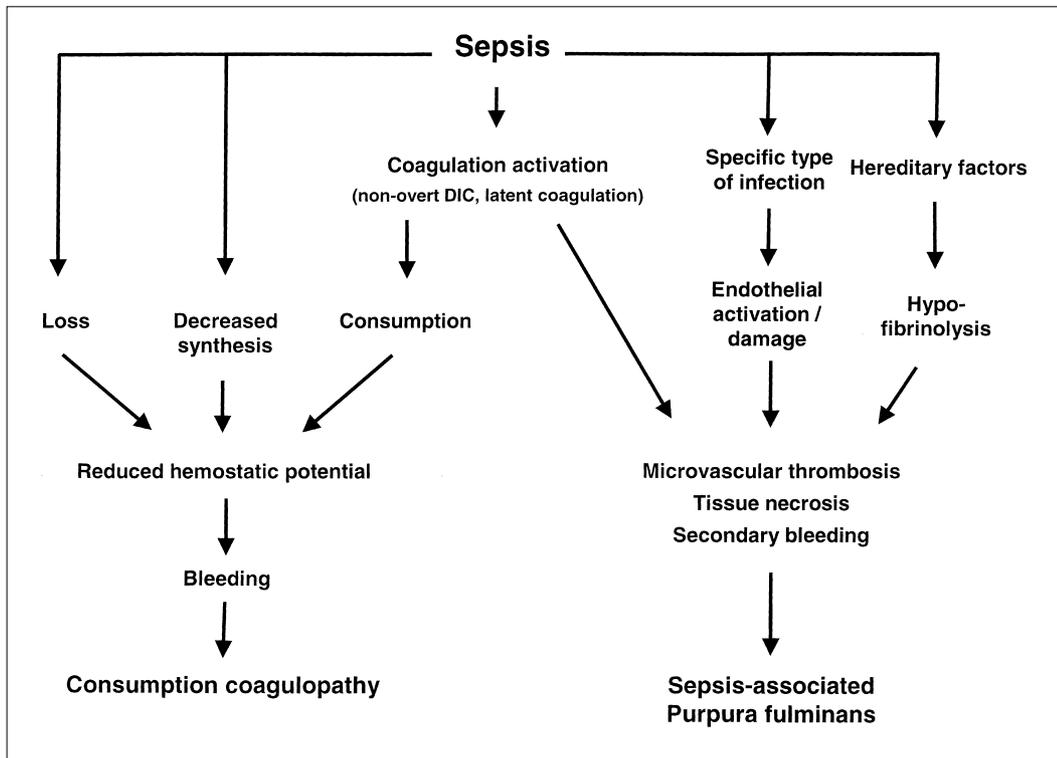
Figure 2: Clinical pathways of coagulation activation in sepsis.

of the skin and various organs (65). The descriptions of purpura fulminans by Waterhouse (66) and Friedrichsen (67) include the following characteristics: sudden onset, fever, cyanosis without dyspnea, purpuric rash, and circulatory collapse. Purpura is a condition of extravasation of cellular blood components into the skin, caused by dermal vascular thrombosis leading to hemorrhagic necrosis (68). Similar changes are observed in various organs, especially the adrenal glands and kidneys (65). Peripheral symmetrical gangrene is a subtype of purpura fulminans mainly associated with pneumococcal, streptococcal, and staphylococcal infections (69, 70). Minor forms, with necrosis of single toes or fingers are observed. Necroses occur despite normal peripheral arterial pulse. Histologic examination typically reveals the presence of thrombi in the small vessels, sparing the large vessels. Occlusion of dermal venules and capillaries by microthrombi causes hemorrhagic infarction (68). Bacteria may be present within the microthrombi, the vessel wall, and the perivascular regions. Surgical reconstructive procedures or amputation of extremities are often necessary (71, 72). Purpura fulminans resembles the experimental Shwartzman reaction induced by two injections of endotoxin given 24 hours apart (73), leading to thrombohemorrhagic skin necrosis and intravascular coagulation. Similar symptoms are found in patients with severe hereditary protein C deficiency (74-76).

Fibrinogen levels were normal in all patients reported by Cohen et al. (71), Churchwell et al. (77), and Escuriola Ettingshausen et al. (78) and in half of the cases reported by Brandzæg et al. (79).

Treatment

Treatment options for coagulation disorders related to sepsis are shown in table 2. Clinical trials aiming at an interruption of 'latent coagulation' in sepsis by administration of coagulation inhibitors such as antithrombin (80-84), heparin (85, 86), gabexate mesilate (87, 88), or tissue factor pathway inhibitor (TFPI) (89-91), have so far failed to demonstrate a statistically significant clinical benefit concerning survival (92), despite the undisputable effect on laboratory indicators of blood coagulation activation or score systems based on such parameters. An exception appears to be drotrecogin alfa (activated) (recombinant human activated protein C)(4) which caused a reduction of the relative risk of death of 19.4% in a large randomized double blind phase III study, at the cost of a slight increase in bleeding complications from 2.0% in the placebo group, to 3.5% in the patients treated with Drotrecogin alfa (activated). Other effects apart from coagulation inhibition seem to be involved in producing the clinical benefit of this treatment (93-95). Treatment with 24 µg/kg body weight per hour Drotrecogin alfa (activated) results in median plasma levels of activated protein C of 44.9ng/ml (96). Taking into consideration the normal level of activated protein C in plasma of 2 ng/ml, treatment with drotrecogin alfa (activated) produces a pharmacologic, not physiologic concentration (96). The clinical effect of Drotrecogin alfa (activated) in sepsis is most pronounced in patients with an expected high mortality such as patients with an APACHE II score of ≥25 (55, 97, 98), multiple organ dysfunction, low plate-

Table 2: Treatment options in sepsis-related coagulation disorders: Evidence from publications.

Substance	Indication	Best evidence
Drotrecogin alfa (activated)	Severe sepsis associated with high risk of death	Randomized, double-blind, placebo-controlled multicenter trial, n=1690 (4)
Drotrecogin alfa (activated)	Purpura fulminans	Case reports (150, 151)
Replacement of coagulation factors and platelets	Consumption coagulopathy	no clinical trials
Recombinant factor VIIa	Severe bleeding in consumption coagulopathy	Case reports (124, 125)
Protein C concentrate	Purpura fulminans	Case reports (78, 137, 141-145, 177-179), Phase II dose finding study (146)
Plasma exchange	Purpura fulminans	Case reports (77, 147)
r-tPA	Purpura fulminans	Case reports (153-156)

let count (55), or advanced age (99). The effect was independent of the causative microorganism (100). Treatment with drotrecogin alfa (activated) leads to more rapid dissolution of organ dysfunction in patients with severe sepsis (101). Drotrecogin alfa (activated) was effective in patients with and without the laboratory criteria of overt DIC (55). In contrast to antithrombin, heparin (102), and other anticoagulant substances (103), Drotrecogin alfa (activated) does not alter endotoxin-induced prothrombin activation and intravascular fibrin formation in the experimental setting (104). On the other hand, protein C-deficient mice develop more severe signs of intravascular coagulation, including more extensive fibrin deposition in the vasculature of various organs in response to the injection of endotoxin than mice with normal plasma protein C levels (105). Drotrecogin alfa (activated) leads to a significant decrease in plasma D-dimer antigen levels in patients with sepsis, indicating reduced intravascular fibrin formation (4). Activated protein C attenuates the inflammatory response by enzymatic action on specific protease-activated receptors (PARs), specifically PAR-1, resulting in decreased NFκB signaling (95).

One randomized prospective double blind study compared human activated protein C (not recombinant) therapy with unfractionated heparin in 104 patients with DIC (106). Death from any cause occurred in 20% of patients treated with activated protein C and 40% of patients treated with heparin (p<0.05). This may either indicate a beneficial effect of activated protein C or a hazardous effect of heparin in the patients studied. Additional data are needed to judge the role of protein C concentrates in the treatment of DIC.

The goal of antithrombin therapy performed in patients with sepsis or DIC was either reaching normal range plasma antithrombin levels or raising antithrombin levels above normal range. Cell culture experiments (107) and various animal experiments (108-110) have shown additional anti-inflammatory effects of supraphysiological concentrations of antithrombin. Blauhut et al. studied a group of 51 patients with laboratory signs of DIC of various causes, 14 of which were patients with sepsis (111). Patients received heparin, antithrombin concentrate, or a combination of both. Overall mortality was 24%, with no difference between groups. Patients with combined antithrombin and heparin therapy displayed increased bleeding. Fourrier et al. treated 35 patients with septic shock and laboratory signs of intravascular coagulation with high doses of antithrombin concentrate or placebo. Treatment with antithrombin concentrate resulted in no statistically significant benefit concerning mortality (80). Langley et al. treated 25 patients with fulminant hepatic failure with antithrombin concentrates or placebo (112) and found no difference in survival between treatment groups.

Other studies of antithrombin substitution (113), antithrombin therapy (114), or combination therapy of antithrombin with heparin (115-117) were purely observational, with no control groups or randomization.

Based on subgroup analyses of a clinical trial (83), animal, and cell culture experiments (118) it is believed that heparin competes with endothelial glucosaminoglycans for the binding of antithrombin, and therefore reduces possible local anti-inflammatory effects of antithrombin. Use of antithrombin concentrate before combined coagulation factor concentrates such as prothrombin complex concentrates (PCC) has been recommended for the prevention of coagulation activation, but no randomized trials addressing this issue have been published. Currently, there is no conclusive published evidence that antithrombin concentrates have an effect on clinical outcome in patients with sepsis, non-overt, or overt DIC.

With the use of sensitive screening techniques, a high rate of venous thromboembolism is found in intensive care patients (119-121). Antithrombin concentrates may be indicated in patients with acquired antithrombin deficiency and thromboembolism, if heparin or other antithrombin-dependent anticoagulants are used. No clinical studies on this indication have been published. Antithrombin concentrates have been used in the perioperative phase in patients with congenital antithrombin deficiency, but no reports have been published on the use of antithrombin concentrate in patients with congenital antithrombin deficiency and sepsis.

Replacement of coagulation factors and platelets represents the most convincing approach for the treatment of a bleeding disorder associated with a deficiency in these compounds, as present in consumption coagulopathy. No systematic studies on the use of fresh frozen plasma, cryoprecipitate, coagulation factor concentrates, fibrinogen concentrate, or platelet transfusions in patients with sepsis-associated consumption coagulopathy have been published. Recommendations are generally based on theoretical assumptions and analogy with inherited or other acquired bleeding disorders. Similarly, the use of antifibrinolytic drugs in consumption coagulopathy is anecdotal (122). There is no evidence from published clinical studies that platelet transfusions and treatment with coagulation factor preparations 'fuels the fire' of intravascular coagulation activation.

Low factor VIIa plasma levels were measured in neutropenic patients with severe sepsis (123). Recombinant factor VIIa has been used for treatment of a variety of severe bleeding disorders and case reports have been published on the use of this drug in patients with consumption coagulopathy (124, 125). Many clinicians will be hesitant to use a massively procoagulant drug in patients with preexisting systemic coagulation activation. Further investigations are needed to clarify if consumption coagulopathy is an indication for the treatment with recombinant factor VIIa.

Bleeding in defibrination syndrome may be due to the absence of adequate amounts of fibrinogen, especially in patients with trauma. Alternatively, it may be the result of fibrinolytic activation, leading to rapid degradation of fibrin clots at vascular lesions. Substitution of fibrinogen by use of fibrinogen concentrates or plasma protein preparations with high concentrations of fibrinogen such as cryoprecipitate (126, 127), may be helpful in bleeding patients with defibrination syndromes. According to the results of Hesselvik et al., treatment with cryoprecipitate does not seem to aggravate coagulation activation in patients with DIC (126). Patients with hyperfibrinolysis may profit from treatment with antifibrinolytic drugs such as tranexamic acid (122, 128). There are no standardized laboratory criteria for the diagnosis of hyperfibrinolysis, making the decision for treatment with antifibrinolytic drugs rather difficult. Additional substitution of factor XIII may be advantageous in patients with deficient wound healing (129), although depletion of factor XIII has been shown to prevent organ damage in an animal model of LPS-induced Shwartzman reaction (130). No randomized trials of fibrinogen- or factor XIII substitution in sepsis, consumption coagulopathy, or defibrination syndrome have been published.

Since microvascular thrombosis is regarded as the predominant pathophysiological feature of purpura fulminans, the majority of therapeutic approaches are aimed at a reduction of coagulation activation and improvement of fibrinolysis. Heparin has been suggested (131-133), but no randomized trials have been published. Antithrombin concentrates have been used

in patients with purpura fulminans (134-136), but again no randomized trials are available.

Patients with purpura fulminans and multiorgan failure in meningococcal infection have significantly higher plasma PAI-1 levels as well as lower protein C and antithrombin levels than patients with meningococcal infection, but without purpura or organ failure (137, 138). In view of the low protein C levels in purpura fulminans (139), numerous case reports of protein C replacement as well as open label studies have been published (78, 137, 140-146). Only a dose of 150 IU/kg body weight or more given every 6 hours resulted in significantly increased levels of activated protein C in patients with purpura fulminans, whereas lower doses failed to cause an increase in activated protein C levels (146). A dose of 600 IU/kg body weight per day increased plasma protein C levels to 2-3 IU/ml and activated protein C levels to three- to fourfold of baseline (146). No effect of protein C concentrate infusion on mortality was found in the phase II dose finding study (146). In the case series published by Escuriola Ettingshausen et al. (78), protein C substitution lead to a rapid decrease in plasma PAI-1 levels. Plasma exchange may be an alternative source of protein C and other plasma components deficient in purpura fulminans (77, 79, 147).

Due to the impaired activation of protein C in severe sepsis (148, 149) it seems logical to use activated protein C in patients with sepsis-induced purpura fulminans. Case reports have been published on the use of drotrecogin alfa (activated) in meningococcal sepsis (150, 151). Activated protein C forms an inactive complex with PAI-1, reducing the functional plasma levels of PAI-1 (152).

An alternative to the inhibition of PAI-1 by activated protein C in purpura fulminans might be treatment with profibrinolytic agents such as tPA (153-156). Only case reports are available and no randomized trials have been performed. A significant proportion of patients treated with tPA suffer from intracerebral hemorrhage, a complication not reported to date for treatment of purpura fulminans with protein C concentrates. Due to these reported cases of intracerebral hemorrhage, it is unlikely that a randomized trial on the use of tPA in purpura fulminans will be performed.

Treatment options: expert suggestions

Heparin / low molecular weight heparin

It has been suggested that treatment with heparin may reduce the anti-inflammatory effect of antithrombin, but no randomized trials comparing patients with sepsis with or without heparin therapy have been published. Due to the high rate of venous thrombosis and pulmonary embolism in ICU patients (157-159), low dose heparin therapy is also standard care in patients with

sepsis. Venous access devices often induce the formation of intravascular clots (160), which may promote bacteraemia (161). Since the bioavailability of unfractionated heparin is reduced in the presence of high levels of acute phase proteins (162-164), low molecular weight heparin is preferred. Bioavailability of unfractionated and low molecular weight heparin given subcutaneously is lower in patients treated with catecholamines due to vasoconstriction (165, 166). A dose of 40mg of enoxaparin (159) or 3800 aXa-units of nadroparin (167) or 5000 aXa units of dalteparin per day are recommended. Unfractionated heparin or low molecular weight heparin for thrombosis prophylaxis may be unnecessary in patients treated with drotrecogin alfa (activated) due to the antithrombotic properties of this drug.

In patients treated with continuous hemofiltration unfractionated heparin, low molecular weight heparin (168) or heparinoids are used. Patients treated with unfractionated heparin receive an initial bolus of 2000-5000 IU of heparin, followed by an infusion of 10IU/kg per hour. Doses are adjusted to maintain an aPTT in the range of 70-80 seconds. When using unfractionated heparin in sepsis patients it should be kept in mind that the activated clotting time (ACT) shows little correlation with the actual level of unfractionated heparin in critically ill patients, and therefore should not be used for treatment monitoring (169). On the other hand the aPTT in patients with sepsis is often prolonged due to low factor XII levels (29). If aPTT prolongation is caused by factor XII deficiency, thrombin time is within normal range. Therefore parallel measurement of aPTT and thrombin time is recommended in sepsis patients treated with therapeutic doses of unfractionated heparin.

For continuous hemofiltration, dalteparin is given as initial bolus of 5-20aXa-units/kg body weight, followed by 5-10aXa-units/kg per hour (168, 170). Similar doses of nadroparin may be used (170). In patients treated with drotrecogin alfa (activated), additional heparin may be unnecessary during continuous hemofiltration (171).

Antithrombin
Antithrombin replacement is indicated in patients with continuous hemofiltration or other extracorporal circulation procedures and low plasma antithrombin levels, if unfractionated heparin or low molecular weight heparin is used for anticoagulation. Target is a normal range antithrombin level. Suggestions for dosages stem from studies on patients with heparin resistance undergoing cardiac surgery (172, 173). Antithrombin levels should be measured daily during continuous hemofiltration or similar procedures. Patients with sepsis and venous thrombosis or pulmonary embolism treated with unfractionated heparin or low molecular weight heparin, as well as patients with hereditary antithrombin deficiency should also receive antithrombin concentrates if the plasma antithrombin level is below 60% of normal. Patients treated with prothrombin complex concentrate (PCC) should receive antithrombin concentrates if the plasma antithrombin level is below 40% of normal.

Drotrecogin alfa (activated)
The approved indication for treatment with drotrecogin alfa (activated) is severe sepsis associated with organ dysfunction, independent of the presence of disseminated intravascular coagulation. Treatment guidelines are therefore focused on the presence of infection, systemic inflammatory response syndrome (SIRS), and organ dysfunction. Clinical score systems, such as the APACHE II score may aid in the selection of patients. A reduced platelet count is regarded as an indicator for the dysfunction of the hemostatic system. Coagulation activation parameters are not taken into consideration. Patients with sepsis-related purpura fulminans or consumption coagulopathy generally fulfill the criteria for adjuvant therapy with drotrecogin alfa (activated), therefore no additional guidelines are needed. Patients are treated with 24 µg/kg body weight per hour for 96 hours.

Protein C concentrate
Beneficial effects of plasma-derived protein C concentrate have been reported in sepsis-induced purpura fulminans. The recommended dosage is 100-600 IU/kg body weight every 6 hours.

Platelets
A reduced platelet count in patients with sepsis may be due to reduced platelet synthesis, blood loss, platelet consumption by coagulation activation, and by hemophagocytosis (174, 175). In the absence of bleeding or other irregularities of coagulation, platelet counts of 5000/µl may be tolerated. In patients with sepsis, the trigger for platelet transfusion should be a platelet count of 20000/µl in the absence of bleeding, and 50000/µl in the presence of bleeding or before invasive procedures or surgery. In patients with severely impaired platelet function, higher levels may be needed. In severely bleeding patients treated with recombinant factor VIIa, the platelet count should be kept above 20000/µl. An optimal dose of platelets has not been established, but typically doses equivalent to five to six random donor platelet concentrates are given initially. Further dosing depends upon the individual response to treatment.

Cryoprecipitate

Cryoprecipitate is a plasma-derived product that contains fibrinogen, factor VIII, von Willebrand factor, and factor XIII. It may, therefore, serve as source for these proteins if purified factor concentrates are not available. One unit of cryoprecipitate per 10kg body weight increases the plasma fibrinogen concentration by 0.4-0.5 g/l.

Fibrinogen concentrate

The threshold for fibrinogen substitution in patients with sepsis-induced coagulation disorders has not been established. Based on personal experiences, fibrinogen substitution may be helpful in patients with active bleeding and plasma fibrinogen levels below 1g/l.

Factor XIII concentrate

Although very low levels of factor XIII are sufficient to induce gamma-chain crosslinking in fibrin, effective wound healing requires higher levels of factor XIII. In patients with trauma or major surgery and inefficient wound healing, factor XIII levels above 50% should be maintained. A single dose of 25-50 IU/kg body weight of factor XIII concentrate is usually sufficient. Higher or repetitive doses may be needed in patients with burn injury or intestinal bleeding.

Fresh frozen plasma (FFP)

In patients with sepsis, prolonged PT and aPTT, and active bleeding or invasive procedures, FFP may be used at a dose of 10-15 ml/kg body weight. Additional doses are given based on clinical and laboratory evaluation. Physiologically tolerable quantities of FFP result only in a 20%-30% increase in the levels of coagulation factors. Due to different plasma half life of coagulation factors, repeated FFP administration may result in an imbalance between coagulation factors with long and short half life. Treatment with FFP may not be sufficient to normalize plasma factor VII levels in patients with sepsis. Plasma exchange has been used in patients with sepsis-induced purpura fulminans (77).

Prothrombin complex concentrate (PCC)

Prothrombin complex concentrates are helpful in bleeding patients with sepsis and vitamin K-deficiency, or as part of a combined strategy involving PCC and fresh frozen plasma. PCC contains coagulation factors II, VII, IX, and X, as well as protein C and protein S. In patients with impaired liver function, PCC may fail to correct an abnormal PT since it does not contain factor V. FFP may serve as source of factor V and other coagulation factors no present in PCC. Doses of 20-30 units/kg body weight of PCC are recommended.

Recombinant factor VIIa

Recombinant factor VIIa may be used in patients with severe bleeding not responsive to other treatment options. Bolus doses of 60-120 µg/kg body weight are given. The bolus may be repeated after 2-6 hours if necessary. If the platelet count is below 20000/µl patients should receive platelet transfusions in parallel since the effect of recombinant factor VIIa is dependent upon an intact platelet surface (176). Patients with head trauma, thromboembolic conditions, stroke or coronary heart disease should not be treated with recombinant factor VIIa.

Desmopressin

Desmopressin (DDAVP or 1-deamino,8-D-arginine vasopressin) stimulates the release of von Willebrand factor, factor VIII, and tPA from endothelial cells, and is used in patients with mild hemophilia A or von Willebrand disease. Desmopressin may cause inappropriate water retention and subsequent hyponatremia. Since plasma levels of von Willebrand factor and factor VIII are typically elevated in patients with sepsis, desmopressin has little effect on bleeding in these patients. Currently, desmopressin cannot be recommended in bleeding patients with sepsis-induced coagulation disorders.

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