REVIEW

Review: Infectious Diseases and Coagulation Disorders

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Infection, both bacterial and nonbacterial, may be associated with coagulation disorders, resulting in disseminated intravascular coagulation and multiorgan failure. In the last few decades a series of in vivo and in vitro studies has provided more insight into the pathogenetic mechanisms and the role of cytokines in these processes. Because of the growing interest in this field, the complexity of the subject, and the fact that many physicians must deal with a variety of infections, current data are reviewed on the association between infectious diseases and the coagulation system. Novel therapeutic intervention strategies that will probably become available in the near future are mentioned, along with those of special interest for infectious disorders for which only supportive care can be given.

Systemic infections may be complicated by activation of the coagulation cascade, varying from subclinical activation, which is indicated by a rise in laboratory markers for thrombin and fibrin generation, to fulminant disseminated intravascular coagulation (DIC) with the formation of microvascular thrombi in various organs [1]. Bleeding, thrombosis, or both may be the presenting clinical features. DIC may contribute to multiorgan failure (MOF) and is associated with a high mortality in both bacterial and nonbacterial disease [2, 3].

Studies of gram-negative sepsis in humans and experimental animals have shown that cytokines play a pivotal role in the activation and regulation of the coagulation cascade, although the interactions are complicated, and the effects are time-dependent and transient [4]. Activation of the coagulation system has also been documented for nonbacterial pathogens (i.e., viruses causing hemorrhagic fevers [HFs] [5, 6], protozoa [malaria] [7, 8], and fungi [9]).

Since no specific effective treatment is yet available for DIC, therapy focuses on treatment of the underlying disorder (e.g., antibiotics for bacterial infection). For many infectious diseases, such as viral HF, causal therapy is not available, and only supportive care can be provided. To improve therapy and supportive care, a better understanding of the pathogenesis of bleeding and thrombotic complications is needed. Novel therapeutic agents that intervene in the coagulation and cytokine cascades will become available in the near future and may have a positive clinical effect, especially for infections for which only supportive care can be given.

Because of the growing interest in this field, the complexity of the subject, and the fact that many physicians deal with a variety of infections, we will review current data on the association between infectious diseases and the coagulation system.

Clinical Aspects of Hemostasis in Bacterial and Viral Infections

Viral and bacterial infections may influence hemostasis and can lead to thrombohemorrhagic complications or syndromes such as DIC, hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP), or vasculitis. Symptoms and signs may be dominated by bleeding, thrombosis, or both.

DIC is an acquired disorder in which the hemostatic system is activated, resulting in activation of platelets and the conversion of fibrinogen to fibrin [3, 10]. This may lead to generalized microvascular thrombosis and MOF and to life-threatening hemorrhage due to consumption of coagulation factors and activation of the fibrinolytic system. DIC as a consumptive coagulopathy, with consumption of both platelets and clotting factors, must be distinguished from the nonconsumptive coagulopathies, such as HUS and TTP, characterized by the consumption of platelets but not clotting factors. HUS and TTP are regarded as variants of a single syndrome characterized by thrombocytopenia, hemolytic anemia, fever, renal abnormalities, and neurologic disturbances. Endothelial injury is consid-

Received 21 September 1998; revised 10 February 1999; electronically published 28 May 1999.

Financial support: KNAW grant (Royal Netherlands Academy of Art and Science, to E.C.M.v.G. and C.S.); and Netherlands Heart Foundation (of which H.t.C. is an established clinical investigator).

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The Journal of Infectious Diseases 1999; 180:176–86

0022-1899/99/8001-0023$02.00

ered the primary event, which, as shown in recent studies, may lead to excessive release of extremely large polymers of von Willebrand factor that cannot be processed to smaller forms because of deficiency of von Willebrand factor–cleaving protease [11–14].

Vasculitis, which may be triggered by infection, is characterized by local or more generalized vascular changes, resulting from infarction secondary to occlusion by thrombi of the lumen of small blood vessels in the upper part of the dermis. Vascular occlusion may lead to ischemic tissue injury due to local vascular occlusion or bleeding due to local tissue damage [15, 16].

None of these syndromes (DIC, MOF, HUS, TTP, or vasculitis) are specific for a certain pathogen, and their occurrence depends on factors such as virulence of the pathogen, the patient's prior condition, source and size of the inoculum, and availability of antimicrobial treatment. For example, these coagulopathic syndromes are encountered more frequently in gram-negative infection than in gram-positive and other nonbacterial infections. Vasculitis (i.e., cytomegalovirus [CMV] vasculitis) occurs in human immunodeficiency virus (HIV)–immunocompromised persons but is rare in persons not immunodepressed, underlining the role of the host's status. There is a relation between the size of the inoculum and the occurrence of the sepsis syndrome, as has been shown in an experimental gram-negative sepsis model in baboons [17].

In some cases of MOF, bleeding and (microvascular) thrombosis may be coexisting features, making it impossible to determine the principal defect (thrombosis or bleeding). Taking these considerations into account, the classification of clinical entities according to bleeding or thrombosis will be the basis for discussion, although the complexity and overlap in clinical presentation must be kept in mind.

Hemorrhage. Hemorrhage may occur as a single clinical phenomenon or may be part of a more complex derangement of the coagulation cascade due to DIC or septic vasculitis, as in gram-negative bacterial sepsis (i.e., meningococcemia [1, 3, 16]). Severity may vary from local defects in hemostasis with oozing from arterial or venous puncture sites to more general complications, such as petechiae, purpura, ecchymosis, gut bleeding, hemoptysis, or even MOF due to adrenal bleeding (as in Waterhouse-Friderichsen syndrome). The clinical signs are not pathogen-specific and in general depend on the severity of infection. In specific infections, such as viral HF, bleeding complications are prominent [18–20]. Among the viral HFs, Dengue [18–20], Marburg [21, 22], and Ebola [23, 24] are the most important. Dengue is the most prevalent (table 1).

Bacterial and viral infections may result in a vasculitis-like syndrome with either bleeding manifestations or ischemic injury [15, 16, 25]. Vasculitis is well documented in CMV infection [26, 27], occurring predominantly in the vasculature of the gastrointestinal tract, where it causes colitis [28, 29]; the central nervous system, where it causes cerebral infarction [30, 31]; and the skin, where it results in petechiae, purpura papules, localized ulcers, or a diffuse maculopapular eruption [32].

HIV infection may be accompanied by vasculitis syndromes, such as polyarteritis nodosa, Henoch-Schönlein purpura, and leukocytoclastic vasculitis [33–36]. Hepatitis B and C infection may cause polyarteritis-like vasculitis [37–39]. Parvovirus B19 has been suggested to be associated with vasculitis-like syndromes, including Kawasaki disease, polyarteritis nodosa, and Wegener's granulomatosis [40–42].

Leptospirosis, especially Weil's syndrome, may present with hemoptysis, epistaxis, intestinal bleeding, adrenal bleeding, hematuria, and even subarachnoid hemorrhage [43]. The pathogenesis may be either primary activation of coagulation or diffuse vasculitis, resulting in bleeding or ischemia of the vascularized tissue. TTP, with bleeding as the presenting symptom, may also occur in the course of Weil's syndrome [44]. In other viral and bacterial infections associated with TTP or HUS, bleeding also is often the prominent and presenting symptom [45–47].

Thrombosis and hemorrhage: DIC. Viral and bacterial infections may theoretically result in local thromboembolic disease, that is, deep venous thrombosis or pulmonary embolism. In a thromboembolic prevention study of low-dose subcutaneous standard heparin for hospitalized patients with infectious diseases, morbidity due to thromboembolic disease was significantly reduced in the heparin group, compared with the group receiving no prophylaxis. There was, however, no beneficial effect of prophylaxis on mortality due to thromboembolic complications [48]. In chronic viral diseases, such as CMV or HIV infection, the risk of thromboembolic complications is relatively low [49, 50].

MOF is a clinical entity characterized by generalized microvascular thrombosis that may develop as part of the DIC syndrome, especially in bacterial gram-negative sepsis but also in

Table 1. Viral infections hallmarked by hemorrhage or viral hemorrhagic fevers (HFs).

Virus	Geographic distribution	Source of infection
Dengue HF	Southeast Asia, Caribbean, Central/South America, China	Mosquito
Chikungunya	Southeast Asia	Mosquito
Ebola	Zaire, Sudan	Unknown
Marburg HF	Zimbabwe, Kenya, Uganda	Unknown
Lassa fever	West Africa	Rodent
Yellow fever	South America, Africa	Mosquito
Omsk HF	Former Soviet Union	Tick
Hantaan	Central Europe, former Soviet Union, Korea, Japan, eastern China	Rodent

severe viral infections. Viral HF (table 1) is complicated by DIC in the most severe cases [18–24]. DIC is not frequently encountered in other viral infections [51, 52] but has been found in cases of rotavirus [53, 54], varicella, rubella, rubeola, and influenza infections [55–61].

TTP and HUS, triggered by a viral or bacterial infection [45–47], frequently lead to bleeding symptoms, as has been discussed, but platelet and fibrin thrombi may also be generated in various organs, leading to prominent symptoms with organ dysfunction. The variety and complexity of the clinical presentation of the coagulopathy syndromes confront the clinician with the difficult questions of whether, when, and how to provide optimal supportive care to combat the coagulation disorders in addition to giving antimicrobial therapy. In making this decision, he or she will probably be guided by the clinically most pronounced presenting symptom.

Principles of Hemostasis, Coagulation, and Fibrinolysis: General Aspects

The hemostatic mechanism consists of primary hemostasis, coagulation, and fibrinolysis (figure 1). Primary hemostasis is maintained by the adhesion and aggregation of platelets to form a hemostatic plug that is stabilized by fibrin strands [62, 63].

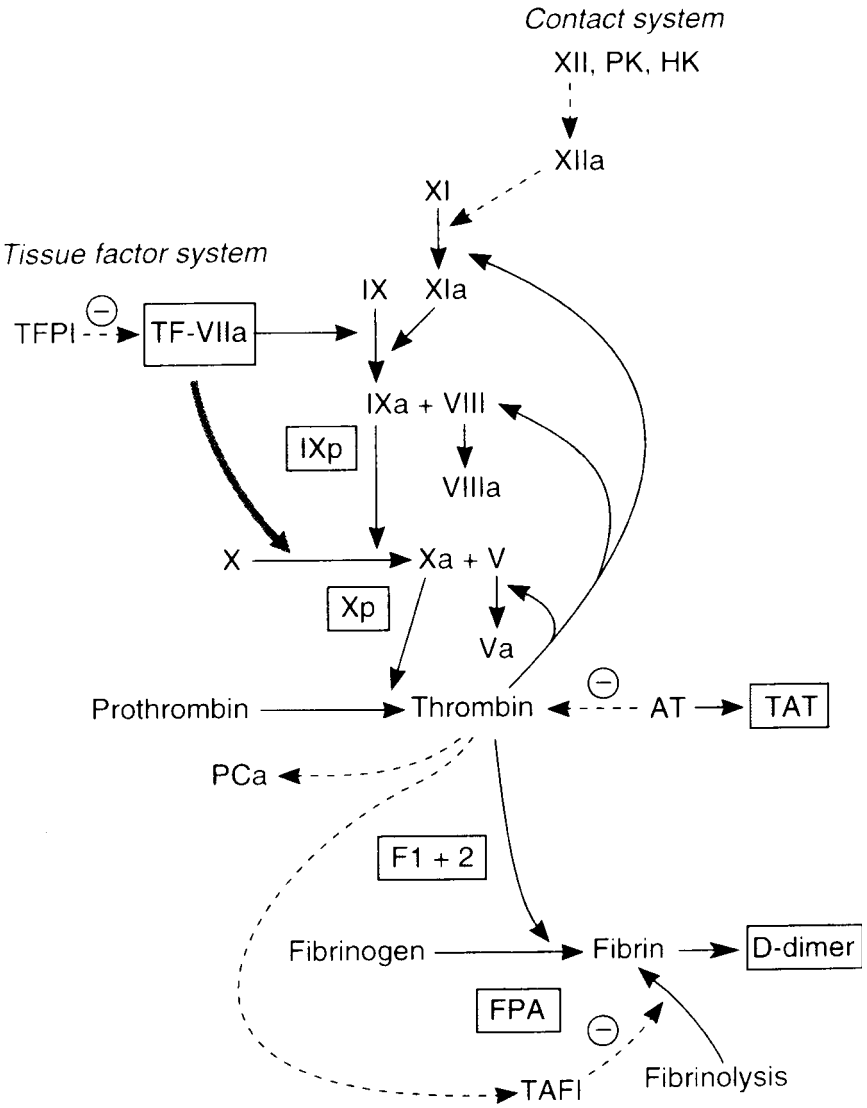

Figure 1. Model of hypothetical coagulation cascade. Products of coagulation activation are shown in squares: IXp, factor IX activation peptide; Xp, factor X activation peptide; F1 + 2, prothrombin fragment 1 + 2; FPA, fibrinopeptide A; D-dimer, fibrin split product; TAT, thrombin-antithrombin complex. Natural inhibitors shown: TFPI, tissue factor pathway inhibitor; AT, antithrombin; PCa, activated protein C (which cleaves activated factors V and VIII). Coagulation proteins are given in roman numerals: PK, prekallikrein; HK, high–molecular weight kininogen; TAFI, recently identified "thrombin activatable fibrinolytic inhibitor."

Coagulation, the second hemostatic defense mechanism, is generated by a series of linked coagulation protease-zymogen reactions, ultimately resulting in the formation of fibrin. In the current concept of coagulation, thrombin generation is induced by the assembly of tissue factor (TF) VIIa complex, the so-called extrinsic route of coagulation.

Coagulation is counteracted by different inhibitory mechanisms. A first mechanism is made up of the circulating inhibitors of blood coagulation, that is, antithrombin, proteins C and S, and TF pathway inhibitor (TFPI). A second inhibitory mechanism consists of the endothelium-bound modulators heparin sulfate and thrombomodulin, which facilitate the inhibitory activity of antithrombin and protein C, respectively. The third mechanism, the fibrinolytic system, is activated by tissue plasminogen activator (tPA) and urokinase after their synthesis and release from the endothelial cell system. These activators initiate the conversion of plasminogen to plasmin, which hydrolyzes polymerized fibrin strands into soluble fibrin degradation products. Infection may lead to an imbalance between platelet function and the regulatory mechanisms of the coagulation cascade and fibrinolysis, resulting in bleeding, thrombosis, or both.

Pathophysiologic Mechanisms of Hemostasis in Bacterial and Viral Infection

On the basis of data from experimental studies that have revealed the complexity of the interactions among infectious pathogens, cytokines, effector cells, and the coagulation system, we will discuss current insights into the pathogenesis of abnormal hemostasis in infectious diseases. Cytokines are thought to play an essential role in activation of the coagulation system during viral and bacterial infections [64, 65].

Coagulation Activation

TF pathway. The TF pathway (extrinsic route) is the main route for activation of the coagulation cascade in sepsis. Endotoxins, lipopolysaccharide constituents of the outer membrane of gram-negative microorganisms, play a pivotal role in the development of the gram-negative sepsis syndrome [66]. Levels of circulating endotoxin are prognostic markers for the clinical outcome of the septic syndrome [67, 68]. Injection of endotoxin or tumor necrosis factor (TNF)–α into healthy volunteers results in activation of the coagulation system via activation of the TF pathway [64, 69–71]. TNF-α injected into volunteers initiates the release of interleukin (IL)–6 and IL-8, which is followed by an increase in the levels of circulating markers of thrombin and fibrin generation (prothrombin fragments [F1 + F2], thrombin-antithrombin complexes [TAT], fibrinopeptide A) [17, 64, 72]. This activation is preceded by a primary but transient activation of fibrinolysis; in contrast, after activation of the coagulation cascade, activation of fibrinolysis is secondary [52]. The net effect of an injection of endotoxin or TNF-α is a procoagulant state. In this experimental model, coagulation and fibrinolysis seem to be activated independently, which may lead to an imbalance between activation of coagulation and regulation (activation/inhibition) of fibrinolysis [73]. The same imbalance has been observed in baboons after injection of IL-1 [74]. Administration of IL-6 into patients with renal cell carcinoma also results in activation of coagulation, as reflected by a rise in the concentration of F1 + F2 and TAT complexes, but here fibrinolysis is not affected [75].

TNF-α induces the expression of TF on monocytes [76] and endothelial cells [77–79]. In chimpanzees and baboons, antibodies directed against TF or factor VIIa or treatment with TFPI prevents activation of the common pathway [71, 80–84], whereas antibodies directed against factor XII do not prevent activation [85, 86], emphasizing the role of the TF pathway. IL-10 can inhibit the coagulant response during systemic infection by influencing the expression of TF on monocytes [87, 88].

As mentioned above, TNF is not an essential factor in the mediation of activation of coagulation in sepsis. This has become evident from studies of volunteers treated with anti-TNF in which endotoxin-induced activation of coagulation did not change [89, 90]. Surprisingly, administration of IL-1ra, a major natural inhibitor of IL-1, results in inhibition of both the coagulation cascade and fibrinolysis in baboons with lethal bacteremia and patients with the sepsis syndrome [74, 91]. Treatment of patients with IL1-ra is associated with decreases in the concentrations of TAT and plasmin-α2 antiplasmin (PAP) complexes and tPA and plasminogen activator inhibitor (PAI)–1 [91]. Treating chimpanzees with anti–IL-6 after the administration of low-dose endotoxin prevents activation of the coagulation cascade but does not affect fibrinolysis [92]. In conclusion, activation of the TF pathway after endotoxin release is largely, although not exclusively, mediated and regulated by cytokines.

Contact activation. Although the factor XII pathway does not seem to play an essential role in activation of the coagulation cascade in experimental sepsis in baboons [85, 86], blocking of the contact activation system by the administration of monoclonal antibodies against factor XIIa could prevent lethal hypotension. This effect is most probably mediated by the generation of kinins, such as bradykinin [85]. Moreover, the contact system seems to play an independent role in the activation of the fibrinolytic system [93]. However, the importance of this route in sepsis has not yet been completely clarified (table 2).

Endothelial Cell and TF Expression

The role of endothelial cells seems to be crucial in the development of shock and activation of coagulation [94–96]. Endothelial cell injury is a common feature of viral infection and can alter hemostasis in a direct or indirect manner. The en-

Table 2. Viruses infecting endothelial cells.

Viruses	
Dengue virus	Herpes simplex virus
Ebola virus	Poliovirus
Marburg virus	Adenovirus
Hantaan virus	Parainfluenza virus
Cytomegalovirus	Echovirus
Measles	Human immunodeficiency virus
Human T cell leukemia virus type 1	Mumps

dothelial cell can be directly infected by different viruses [97–99], for example, herpes simplex, adenovirus, parainfluenzavirus, poliovirus, echovirus, measles, mumps [100], CMV [101], human T cell leukemia virus type 1 [102], and HIV [103]. The ability to infect endothelial cells has also been demonstrated in HFs caused by Dengue, Marburg, Ebola, Hantaan, and Lassa viruses [104]. Such infections may result in a procoagulant state, mainly by inducing TF expression on the endothelial surface [105–107], probably mediated by cytokines such as IL-1 [105–112], TNF-α, and IL-6 [113–115].

An additional cause of enhanced coagulability may be prothrombinase complex assembly on the CMV surface [116]. This observation suggests that the CMV surface contains the necessary procoagulant phospholipids for assembly of the coagulation enzyme complex leading to thrombin generation. A similar observation has been made for HIV [117]. However not all viral infections affecting endothelial cells result in activation of coagulation, which may indicate that activation of endothelium is one factor in a multifactorial process (figure 2).

Fibrinolysis

General aspects. The process of fibrinolysis involves the enzymatic cascade, which helps to break down cross-linked fibrin molecules. Fibrinolysis may be activated primarily—and thus independently of activation of the coagulation cascade—or secondarily in response to fibrin formation. If fibrinolysis is not balanced in time and scope, either bleeding or thrombosis may ensue. After the injection of TNF into healthy volunteers, activation of the coagulation cascade is preceded by a transient activation of fibrinolysis, which is reflected by increased circulating levels of tPA and urokinase plasminogen activator, followed by an increase in PAI-I, suppressing fibrinolysis [64, 72, 118, 119]. Coagulation activation triggers a secondary activation of fibrinolysis [52], which is rapidly shut off by the release of relatively large amounts of PAI-I, such that the net effect of the injection of a bolus of endotoxin is a procoagulant state.

Infusion of IL-1α into baboons also elicits an early and tran-

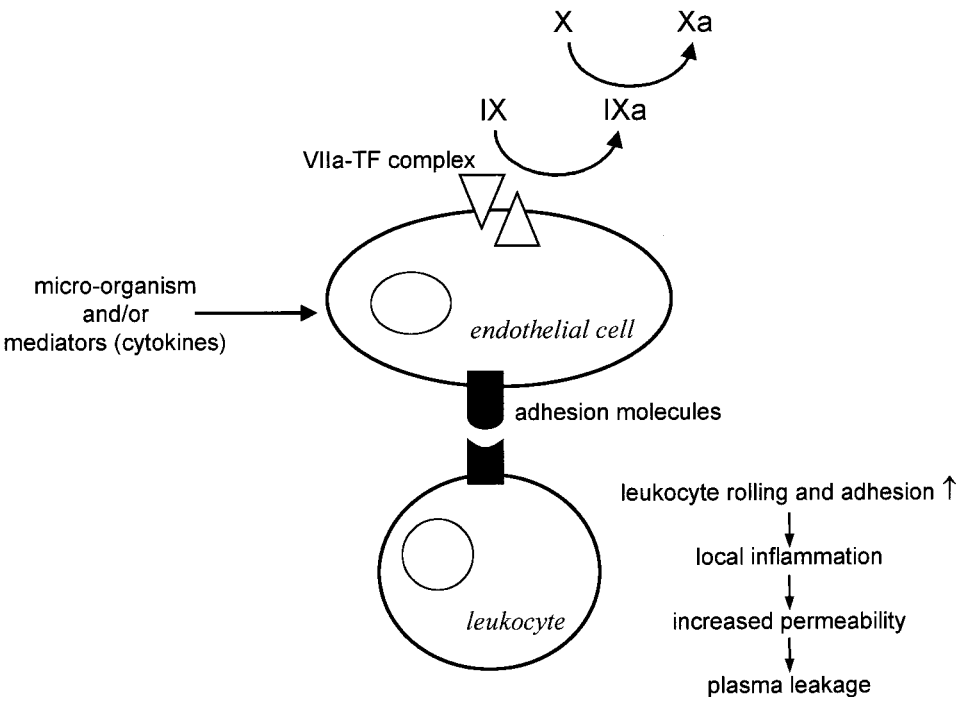

Figure 2. Endothelial cell in infection. During infection, endothelial cell may change to procoagulant state by expressing tissue factor on membrane. Tissue factor is main inducer of extrinsic pathway of blood coagulation. Increased endothelial permeability resulting in plasma leakage may be the consequence of local or more generalized inflammatory response, with increased leukocyte adherence to endothelial cell. This mechanism is triggered by up-regulation of endothelial cell adhesion molecules (i.e., intercellular adhesion molecule 1, vascular cell adhesion molecule 1, E-selectin, P-selectin).

sient activation of fibrinolysis [74] followed by the production of PAI-1, leading to a balance. Fibrinolytic activation is followed by activation of coagulation, thus showing the same imbalance between coagulation and fibrinolysis observed after the administration of TNF-α. This procoagulant imbalance is also present in DIC, where the net effect will be a tendency toward diffuse bleeding and microvascular thrombosis.

Treatment with anti-TNF in the human and chimpanzee sepsis models inhibits the fibrinolytic system, as reflected by the absence of a rise in tPA, PAI-1, and PAP complexes [89, 90, 120], whereas coagulation is not affected, showing that TNF plays an important role in regulation of the fibrinolytic response. Administration of IL-1ra into baboons with lethal bacteremia or patients with sepsis inhibits both coagulation and fibrinolysis [74, 91], as indicated by decreased concentrations of TAT and PAP complexes and tPA and PAI-1 [91]. Treating chimpanzees with anti–IL-6 after the administration of low-dose endotoxin prevents activation of the coagulation cascade and does not affect fibrinolysis [91].

Protein C/S system. During sepsis, the protein C/S system is down-regulated [121]. After the release of TNF-α, thrombomodulin is also down-regulated, resulting in a further decrease in protein C activity, thereby enhancing the procoagulant state. Some viruses can induce specific changes in the coagulation inhibitory system. During the course of HIV infection, the protein C/S system may be impaired as a result of an acquired protein S deficiency, the pathogenesis of which is not yet clarified [122–125]. In children, protein S deficiency seems to correlate with the duration of HIV infection [122], but such a relationship has not been found in adults [123]. Increased plasma concentrations of the C4b-binding protein, an acute-phase protein that binds protein S, may result in decreased levels of free protein S. Antiphospholipid antibodies, which may be present in persons infected with HIV, might interfere with the protein C–protein S complex and diminish its activity [123, 126–129]. In patients with Dengue HF, we also found decreased levels of both protein C and protein S activity (current authors, unpublished data). As in Dengue infection, HIV can affect the endothelial cell; hypothetically, this could lead to decreased production of protein S.

Thrombocytopenia

Thrombocytopenia is seen in the course of many viral infections but is only occasionally serious enough to lead to hemostatic impairment and bleeding complications [130]. It is assumed that thrombocytopenia is mainly immune mediated [131]. The mechanism is decreased thrombopoiesis [132, 133], increased platelet consumption [134], or a combination of both. Direct interaction of the virus with platelets [5, 135, 136] may lead to thrombocytopenia or thrombocytopathy. Endothelial injury by the virus [137] may lead to increased adherence and consumption of platelets [138].

Viral infections that have been associated with thrombocytopenia are mumps [139, 140], rubella [141–143], rubeola [144], varicella [145–147], disseminated herpes simplex [148], CMV infection [149, 150], infectious mononucleosis [151–155], Hantaan virus infection [156, 157], Dengue HF [5, 135, 158], Crimean-Congo HF [159], and Marburg HF [160]. Dengue fever is associated with thrombocytopenia even in mild and uncomplicated cases [5]; therefore, thrombocytopenia cannot be the only explanation for the occurrence of bleeding.

Soluble Adhesion Molecules

The change of the endothelial cell from a resting to a procoagulant state may be associated with expression of endothelial surface adhesion molecules [112, 161, 162]. These molecules, that is, the intercellular adhesion molecule, the vascular cell adhesion molecule, E-selectin, and the von Willebrand factor, play an essential role in the binding of leukocytes, resulting in a local inflammatory response, endothelial cell damage, and subsequent plasma leakage and shock [163–166]. Vasculitis also occurs and has been documented in association with such viruses as CMV and HIV [26, 167, 168]. The finding of increased plasma concentrations of these endothelial surface adhesion molecules is thought to reflect the level of activation and perhaps damage of the endothelial cell. Measuring circulating endothelial cells by immunofluorescence or immunomagnetic separation may provide additional information about the activation of vascular endothelium [169–171].

Conclusions

Infectious diseases are often accompanied by activation of coagulation. Although direct interactions between the infectious agent and the coagulation system occur, cytokines are believed to be important mediators in this process. During systemic gram-negative and gram-positive bacterial infections, activation of coagulation is mediated via the extrinsic TF pathway. Experimental studies suggest that, as a rule, coagulation and fibrinolysis occur independently of one another, and the overall result is usually a procoagulant tendency. The latter may result in DIC with microvascular thrombosis and organ failure. Bleeding may result from consumption of platelets and clotting proteins in traumatized tissues.

Although this scenario has been derived largely from studies with purified endotoxin or gram-negative bacteria, we expect similar alterations to occur in gram-positive and in specific viral infections, because some of the key intermediate cytokines (TNF, IL-1, IL-6) are involved. It should be noted, however, that the mechanisms by which viruses presumably induce coagulation in vivo are still speculative, since only in vitro data are available. The critical cellular elements involved in these reactions may not be the same for bacterial and viral infections, but we speculate that the vascular endothelium is a main target.

Endothelial cells may turn into a procoagulant state either by stimulation of cytokines in concert with circulating blood cells, such as lymphocytes or platelets, or by direct infection (viruses) of endothelial cells.

Bleeding in infectious disease is most likely a multifactorial process resulting from a combination of thrombocytopenia, consumption of clotting factors, (local) hyperfibrinolysis, and vascular damage or leakage. In addition, immunologically mediated vasculitis may contribute to bleeding in specific infections.

The clinical consequences of chronic viral infections (e.g., CMV and HIV) for the development of thrombotic complications, vasculitis, and atherosclerosis are of great interest. One could hypothesize that since CMV infection may lead to transformation of the endothelial cell to a procoagulant state but may also induce vasculitis and atherosclerosis [172], there could well be a common pathway in the pathophysiologic mechanism of these physiologic and anatomic entities. The role of other pathogens, such as *Chlamydia pneumoniae* that have the potency to affect the endothelium and contribute to the pathogenesis of atherosclerosis is of interest [173–175].

Knowledge of the underlying mechanisms leading to thrombosis or bleeding is fundamental for the development of therapeutic strategies. In gram-negative infections, insight into the important roles of endotoxin and specific cytokines has already led to clinical therapeutic trials with selective inhibitors of the TF pathway (monoclonal antibodies, Fab fragments, modified factor VIIa, nematode anticoagulant protein, TFPI) [176, 177]. Studies with anti-TF antibodies and TFPI in primates have shown that, in addition to inhibition of coagulation activity, these agents may have significant anti-inflammatory properties and may markedly reduce mortality in otherwise lethal infections [178, 179].

Given the potential role that endothelial TF may play in some of the thrombohemorrhagic complications of viral disease, we expect that therapeutic intervention at the TF level or aimed at one of the critical cytokines that mediate its cellular expression may potentially favorably alter the clinical course of these infections. Many issues remain to be answered, and thus there is an urgent need for more clinical and experimental studies, particularly with respect to the relationship between viral infections and the mechanisms leading to bleeding/DIC. Needless to say, treatment of the causal infectious agent remains the cornerstone of therapy.

Acknowledgments

In addition to the authors, the following persons were project participants: R. Djokomoeljanto, University of Diponegoro, Semarang, Indonesia; L. W. Statius van Eps, Department of Internal Medicine, Slotervaart Hospital, and Free University, Amsterdam; C. E. Hack, Central Laboratory of the Blood Transfusion Service, Amsterdam; J. Sutaryo and M. Juffrey, Gadjah Mada University, Yogyakarta, Indonesia; L. G. Thijs and A. J. P. Veerman, Free University, Amsterdam.

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