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# Infectious agents including COVID-19 and the involvement of blood coagulation and fibrinolysis. A narrative review

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**Abstract. – OBJECTIVE: Platelets, blood coagulation along with fibrinolysis are greatly involved in the pathophysiology of infectious diseases induced by bacteria, parasites and virus. This phenomenon is not surprising since both the innate immunity and the hemostatic systems are two ancestral mechanisms which closely cooperate favoring host's defense against foreign invaders. However, the excessive response of these systems may be dangerous for the host itself.**

**MATERIALS AND METHODS: We searched and retrieved the articles, using the following electronic database: MedLine and Embase. We limited our search to articles published in English, but no restrictions in terms of article type, publication year, and geography were adopted.**

**RESULTS: The hemostatic phenotype of the infectious diseases is variable depending on the points of attack of the different involved pathogens. Infectious diseases which show a prothrombotic phenotype are bacterial sepsis, SARS-CoV-2 and malaria. However, among the bacterial sepsis, Yersinia Pestis is characterized by a profibrinolytic behavior. On the contrary, the hemorrhagic fevers, due to Dengue and Ebola virus, mainly exploit the activation of fibrinolysis secondary to a huge endothelial damage which can release a large amount of t-PA in the early phase of the diseases.**

**CONCLUSIONS: Blood coagulation and fibrinolysis are greatly activated based on the strategy of the different infectious agents which exploit the excess of response of both systems to achieve the greatest possible virulence.**

*Key Words:*
Bleeding, Thrombosis, nCoV-19, Sepsis, Malaria, Ebola virus.

## Introduction

Platelets, blood coagulation along with fibrinolysis are greatly involved in the pathophysiology of infectious diseases induced by bacteria, parasites and virus[1]. However, the phenotype of these diseases may vary depending on the point of attack at the hemostatic system by the different pathogens involved. It is important to know which infectious diseases can induce a disseminated intravascular coagulation (DIC)[2] characterized by either bleeding (hyper-fibrinolysis phenotype) or microvasculature thrombosis (thrombotic phenotype) depending on whether coagulation or fibrinolysis pathway is activated[3]. Furthermore, virus and bacteria may involve the hemostatic system, thus contributing significantly to the severity of the clinical course of the infection. The aim of this narrative review is to describe how bacteria, virus and parasites work. Knowing these mechanisms can be helpful in the management of different infectious diseases since either anticoagulants or anti-fibrinolytic drugs may counteract the different clinical coagulation abnormalities of these conditions.



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## Materials and Methods

We carried out a narrative review on the topic of infectious disease and coagulation. To search for articles, which addressed the review topic, we used an electronic-based strategy. We searched and retrieved the articles, using the following electronic database: MedLine and Embase. We limited our search to articles published in English language, but no restrictions in terms of article type, publication year, and geography were adopted.

A combining keyword searching strategy was used to narrow results. We identified and chose following keywords and search strategy: "virus" OR "bacteria" OR "parasites" AND "thrombosis" OR "hemorrhage" OR "fibrinolysis" AND "outcome". We assessed the relevance of published articles included in this review by defining inclusion criteria of literature selection. Articles were preliminarily defined as eligible if they a) were directly related to the review topic, b) had clear statement of aim, c) were published in peer-reviewed journals, and d) were in English. A first level screening of articles extracted from electronic databases was done by reading titles and abstracts. Subsequent critical assessment of full-text eligible articles was based on appraisal of relevance of topic, defined clinical questions, study methodology, description of findings, and significance and possible impact of the findings on review topic. Attention was paid to exclude duplicate articles.

## Results

### Thrombotic Phenotype (But Not Always)

In sepsis DIC represents a severe complication. Briefly, bacterial fragments, i.e., lipopolysaccharide (LPS), activate monocytes which release several cytokines (IL-1, IL-2, IL-6, TNF etc.) that, in turn, induce an endothelial damage. Tissue Factor (TF) is exposed on the cell membrane of monocytes after the contact with LPS. Blood coagulation is activated, and thrombin is hence generated. Platelets' activation by thrombin *via* PAR is another crucial step which further concours to develop a thrombotic process[4]. During sepsis, the von Willebrand factor-cleaving protease (ADAMTS13) is much less expressed on the endothelial cells so that von Willebrand factor can further activate platelets[5]. On the other hand, thrombocytopenia often is the first sign of an overt DIC because platelets are early involved in the defensive cooperation with neutrophils trying to limit and possibly eliminate foreign invaders. Sepsis induces the activation of neutrophils which leads to the formation of neutrophil extracellular traps (NETs) consisting in DNA, histones, and antimicrobial proteins, aiming to kill bacteria and virus[6]. NET can activate both the intrinsic and the extrinsic pathway of blood coagulation, thus inducing fibrin deposition in the microvasculature (Figure 1)[7]. Fibrin binds to inflammatory cells *via* the Toll-like receptor 4. Inflammation is thus further enhanced through the release of cytokines which, in turn, affects both blood coagulation and fibrinolysis[8]. The levels of plasminogen activator inhibitor 1 (PAI-1) increase, inducing a fibrinolysis shutdown. This phenomenon is coherent with the aim of entrapping bacterial into a mesh of fortified fibrin. The final result is a DIC characterized by a thrombotic phenotype[9,10]. In contrast, Yersinia Pestis (YP), a gram-negative bacterium responsible of plague, is able to activate fibrinolysis. Plague is a severe disease not completely disappeared in the world, transmitted by a fleabite but infection can also be suffered by both the inhalation of contaminated aerosols and the ingestion of infected food, as it has been recently reported[11]. YP has a trans-membrane protein, plasminogen activator (Pla), which can modulate fibrinolysis by the activation of plasminogen to plasmin thus significantly getting help in its widespread once entered the cutis by a fleabite which carries the bacteria coming from infected rats and marmots[12]. This mechanism allows YP to obtain a breakdown of the extracellular matrix thus overcoming the innate immunity since fibrin has a role not only in the restraining the bacterium but also in contacting inflammatory cells to build an optimal abscess morphogenesis. However, YP is also able to activate, even in a very weak way, blood coagulation perhaps because fibrin formation can initially be protective from host defensive mechanisms (Figure 2)[13,14]. An alternative pathway may consist in the activation of fibrinolysis by fibrin since its fibers, tPA and plasminogen form a tertiary complex which can activate fibrinolysis thus further enhancing the proteolytic properties of the infectious agent[15]. Fibrin formed in this way showed to be soluble in 5 M urea so indicating a poor cross-linking by factor XIII possibly because of the enhanced activity of the plasminogen activator during

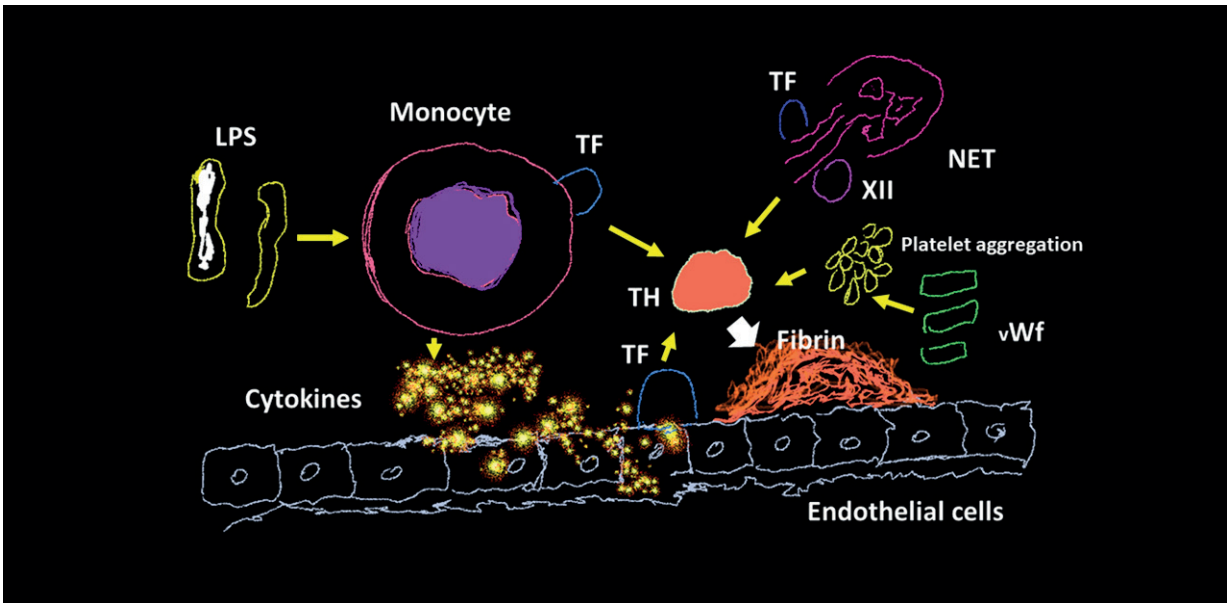


**Figure 1.** Bacterial fragments (LPS) activate monocytes which release a number of cytokines (IL-1, TNF etc.) that in turn induce an endothelial damage. Tissue Factor is exposed on the cell membrane of monocytes after the contact with LPS. Blood coagulation is so activated. Fibrin deposition occurs. Platelet aggregation induced by von Willebrand factor, released by damaged endothelial cells, further enhances blood clotting. Neutrophil Extracellular Traps release histones, DNA and enzymes for killing bacteria. They can activate blood coagulation via both intrinsic and extrinsic pathway so contributing to clot growth. *Abbreviations:* LPS= Lipopolysaccharides, TF= Tissue factor, NET= Neutrophil Extracellular Traps, Th=Thrombin, vWf= von Willebrand Factor, XII= factor XII.

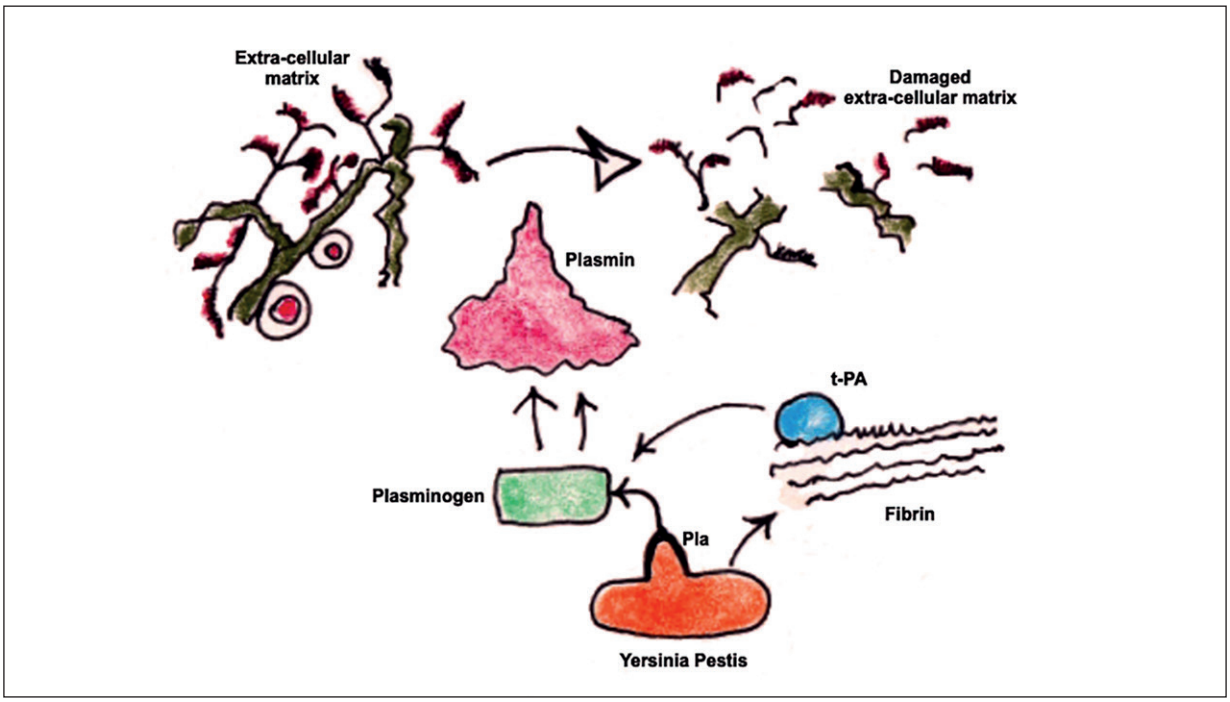


**Figure 2.** This Gram - bacterium has a receptor (Pla) which is able to activate plasminogen to plasmin. The result is a breakdown of the extra-cellular matrix which allows the widespread of this infectious agent. Yersinia pestis is also a weak activator of blood coagulation but this property is functionally important for a further fibrinolysis activation. *Abbreviations:* Pla= Plasminogen activator, t-PA= Tissue Plasminogen Activator.

clotting[16]. Again, Pla carried by YP has been found to degrade thrombin activatable fibrinolysis inhibitor (TAFI) closing another way to clot stabilization[17]. Recently Assinger et al[18] point out the role of YP in the platelet's involvement described by Palace et al[19]. These authors describe how YP inhibits platelet aggregation leading to both thrombi destabilization and an impairment of platelet-neutrophil cross-talk adding a further mechanism aimed to minimize the role of the hemostatic system.

### nCoV-19

Novel Coronavirus (nCoV-19) is an RNA virus with an envelope along with a glycoprotein and spike protein. It is a respiratory virus which enters the lungs using angiotensin converting enzyme 2 (ACE2) as a receptor[20-22]. The binding of the spike S1 protein of nCoV-19 to ACE2 induces endocytosis with subsequent translocation of the virus into the cells. This mechanism is common to other Corona virus[23]. The consequence is a direct cytopathic effect of nCoV-19 on the pneumocytes, inducing a release of cytokines and the activation of monocytes which in turn produce a further amount of cytokines on one hand and the expression of tissue factor, the trigger of blood coagulation, on the other[24]. In other words, a DIC may occur as suggested by Tang et al[25] who found the International Society of Thrombosis and Hemostasis (ISTH) criteria for DIC in 71.4% of non-survivors and in 0.6% of survivors infected by nCoV-19. However, these authors did not report any bleeding thus indicating an important blood coagulation activation but not an overt DIC which is characterized by microcirculation thrombosis and secondary bleeding due to clotting factors and fibrinogen consumption[26]. Hence, we proposed that the abnormal laboratory findings found by Tang et al[25] could be the expression of a local DIC, i.e., a pulmonary thrombosis[27]. A confirm of this assumption has come later from the autoptic findings by Dolhnikoff et al[28] and Lax et al[29] who demonstrated thrombosis in small and mid-sized pulmonary arteriole. On the other hand, the concept of "pulmonary thrombosis" has been recently advanced, before the nCoV-19 era, for pneumonia, asthma, chronic obstructive pulmonary disease, Gaucher disease, sickle cell disease and assisted reproductive technologies[30]. Moreover, Acute Respiratory Distress Syndrome (ARDS), a frequent and severe complication of the nCoV-19 disease, may be associated with pulmonary vascular microthrombosis[31], further confirming that a local pulmonary thrombosis may occur during nCoV-19 infection. However, ACE2 expression has been found in many other tissues, including endothelial cells which can be severely affected by nCoV-19[32]. A so important damage may explain the development of deep vein thrombosis and pulmonary embolism, other than pulmonary thrombosis, detected in a high percentage in patients with nCoV-19 infection. Ward et al[33] demonstrated that in patients with severe nCoV-19 infection, the von Willebrand factor pro-peptide is greatly increased in these patients and that its values are well correlated with the severity of the disease showing a relationship with sequential organ failure assessment (SOFA) and sepsis-induced coagulopathy (SIC) scores. Nevertheless, nCoV-19 infection may be dangerous also in the arterial side because it can be able to provoke the dysregulation of the renin-angiotensin system thus inducing endothelial dysfunction which can favor the invasion of the plaque by inflammatory cells along with intra-plaque hemorrhage. These pro-thrombotic mechanisms could explain why subjects with nCoV-19 infection may suffer from ischemic stroke even at a young age[34]. The role of fibrinolysis is interesting to know in this setting. Coccheri[35] recently pointed out the opposite role of fibrinolysis during nCoV-19 infection based on a local fibrinolysis behavior. Sites of locally increased t-PA, such as the alveolar space, may suffer from bleeding while in sites where PAI-1 is increased, micro-thrombosis and an outcome towards pulmonary fibrosis may be a dominant phenomenon. However, fibrinolytic shutdown is now recognized during nCoV-19 infection. In this setting, a crucial role of ACE2 is to be acknowledged. An increased amount of uncleaved Angiotensin II due to the downregulation of ACE2 after the binding with nCoV-19, significantly increases PAI-1 thus inducing an unbalance favoring a prothrombotic condition[36]. An impaired fibrinolysis was also found by Wright et al[37] who measured clot lysis by a viscoelastic method in 44 patients with nCoV-19 infection admitted to an intensive care unit (ICU). A lack of clot lysis at 30 minutes was detected in 57% of these patients and was predictive of venous thromboembolism with a significant area under the curve (0.742, $p$=0.021). This finding along with a D-Dimer level > 2600 ng/ml predicted both a thromboembolic event and dialysis. Again, high D-dimer levels were found by Pan-

igada et al[38] in patients admitted to an ICU but with a concomitant hypercoagulable state detected by means of a thromboelastography point of care device.

A question arises: why so high D-Dimer levels are found with both a hypercoagulable state and a fibrinolysis shutdown? It is worth noting that D-Dimer comes from both intravascular and extravascular fibrin. It is known that this test is characterized by a high sensitivity and low specificity[39]. This seems the case of patients with nCoV-19 infection who suffer from a pneumonitis which can be the source of D-dimer coming from extensive alveolar fibrin deposition[40]. Also, in nCoV-19 infection the role of NET is important. Petito et al[41] recently demonstrated that NET biomarkers, more than platelets, were correlated with the severity of the disease and with venous thrombotic events. In addition, NET biomarkers did not normalize after recovery and their formation was blocked by therapeutic dose of LMWH.

## Parasites and DIC

### *Malaria*

Malaria is an important parasitic disease which affects million people each year with high mortality rates which result to be significantly reduced from 2005 to 2017 by 42.5%. In the same period malaria cases due to Plasmodium falciparum declined from 232·3 to 193·9. If it is true that malaria is a disease of tropical countries, many cases exported by travelers have been recorded all over the world[43]. Plasmodium falciparum infections are more common among children aged 5-15 years than among younger children and adults[44]. While bleeding is unusual unless the disease is extremely severe, thrombosis is commonly found. Fibrin thrombi have been detected in skin biopsies of patients and, post-mortem, in the microcirculation of several apparatus[45]. These findings have been interpreted as an outcome of a DIC but, as it happens in bacterial sepsis, it is characterized by a fibrinolysis shutdown. Plasma levels of PAI-1 were found to be significantly higher in Plasmodium Falciparum infection when compared with those of the controls. Monocyte procoagulant activity was found to be very high, thus indicating the presence of a hypercoagulable state[46]. Nevertheless, other mechanisms further enhance this prothrombotic scenario: parasitized red blood cells (RBC) adhere to the endothelial cells inducing a damage which, in turn, stimulates TF exposition on these cells (Figure 3). Phosphatidylserine is then exposed on the parasitized RBC, thus inducing clotting factors adsorption, ready for clotting[47]. Moreover, von Willebrand factor is released from damaged endothelial cells causing platelet activation which significantly contributes to thrombus growth[48,49]. All these mechanisms are involved in the patho-

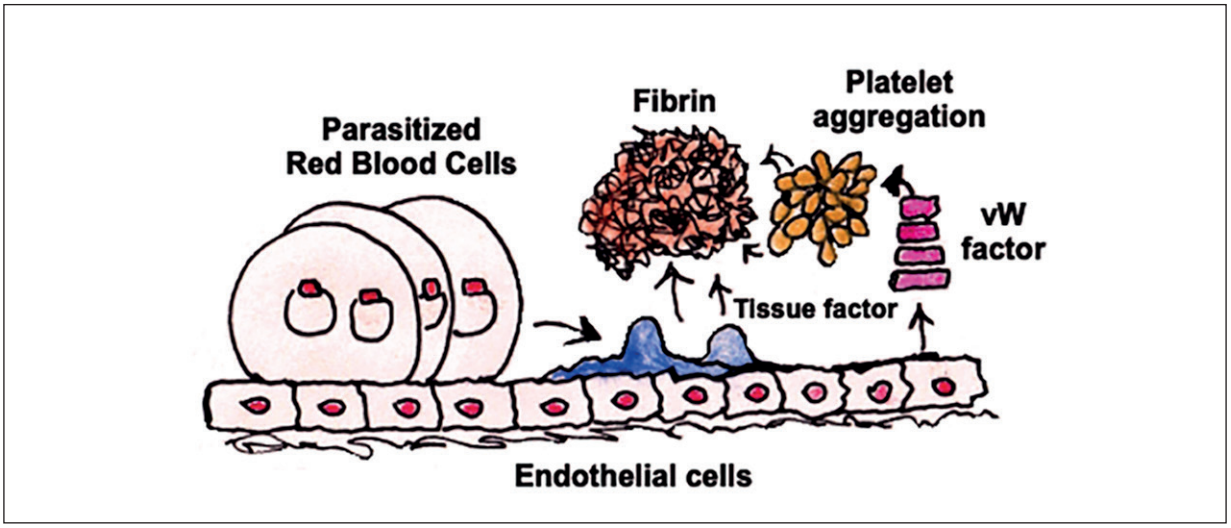


**Figure 3.** Parasitized RBC adhere to the endothelial cells inducing a damage which in turn stimulates Tissue Factor exposition on these cells. Blood coagulation is also activated by Phosphatidylserine exposed on the parasitized RBC. Clotting factors are here adsorbed and then ready to form fibrin. Blood coagulation is so activated. von Willebrand factor is released by damaged endothelial cells. ADAMTS 13 is so consumed. Platelet activation occurs contributing to blood clot formation. *Abbreviations:* vW factor= von Willebrand factor.

genesis of cerebral malaria (CM) which may be fatal especially in children. The findings of Moxon et al[50] indicate that the derangement of the Protein C pathway and the abnormal fibrin deposition in the cerebral microvasculature may play a crucial role in this setting. These authors found important abnormalities of coagulation whose magnitude is related to mortality. Finally, the same group recently found that in CM circulating extracellular histones, of host and parasite origin, were increased in CM patients showing an association with brain swelling detected by magnetic resonance imaging. Moreover, histones were found to be colocalized with Plasmodium Falciparum infected erythrocytes in the microvasculature on post-mortem brain section. This phenomenon was associated with thrombosis and leakage thus suggesting a link between accumulation of histones and both blood coagulation activation and brain blood barrier breakdown[51].

### Hemorrhagic Phenotype

Dengue Fever (DF) is caused by an arthropod-born virus which belongs to the Flaviviridae family. This RNA virus is transmitted by the *Aedes aegypti* mosquito[52]. About 50 million individuals are infected each year while 2.5 billion live in endemic areas[53]. Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) are the two most severe forms of DF. The first one is characterized by endothelial injury which induces plasma leakage and shock leading to DSS. Bleeding is an effect of hemostasis activation with a secondary hyperfibrinolysis. However, fibrinolysis may be activated also by the endothelial damage itself which releases tissue-Plasminogen Activator (t-PA) in a much more amount than that of PAI-1 in the acute phase of the disease. Huang et al[54] found in a small group of patients thrombocytopenia, APTT prolongation, and t-PA increase in the acute phase of the disease, suggesting activation of coagulation and fibrinolysis. In particular, the activation of coagulation and fibrinolysis in DHF/DSS was much more severe than in DF patients. The t-PA/PAI-1 ratio in the acute stage of DHF/DSS patients was at least 2-3-fold higher than that observed in the acute stage of DF patients. This figure was reversed in the convalescent stage: PAI-1 level and platelet count rose concomitantly to the reduction of t-PA level while APTT returned to normal in both DHF/DSS and DF patients. Orsi et al[55] published a case-control study that involved 33 patients with DF without bleeding and 26 adults with DF and bleeding complications during the defervescence period. A control group of 67 healthy controls was included in the study. The authors carried out peripheral blood counts, inflammatory, fibrinolysis and endothelial cell activation indicators along with thrombin generation. Interestingly, both levels of t-PA and D-dimer were significantly increased in bleeders in comparison with those without bleeding and controls. Thrombocytopenia and a reduced thrombin generation were also detected in patients with bleeding complications in comparison with those without bleeding and controls. If on one hand a consumption coagulopathy occurs in patients with DF, due to the activation of monocytes, a target of the Dengue Virus, it also quite clear that a hyperfibrinolysis state overcomes that of the activation of coagulation on the other. Dengue virus enters the monocytes inducing a release of cytokines and the exposition on their membrane of TF, the trigger of blood coagulation activation but the activation of fibrinolysis is not only due to fibrin deposition but also, and mainly, to the release of t-PA coming from the direct endothelial damage induced both by the virus and the cytokines storm[56]. The clinical feature of the disease is therefore a severe hemorrhagic syndrome.

### EBOLA Virus

Ebola (EBV) and Marburg viruses belong to the Filoviridae family of RNA viruses. They can cause hemorrhagic fever (HF) in humans, with high mortality rates[57]. Patients with filoviral HF may show mucosal bleeding along with easy bruising and persistent bleeding from sites of injection or venipuncture. Although hemorrhage is not present in all patients, severe bleeding is observed in fatal cases typically in the gastrointestinal tract. Intracranial hemorrhage has also been described[58]. EBV, as Dengue virus, with its envelope Glycoprotein C enters monocytes and dendritic cells thus promoting its own replication. They are then released by monocytes carrying TF exposed by these cells and their Glycoprotein C. Both activate blood coagulation[56]. Cytokines' production by monocytes, along with TF, is relevant on one hand while the activities of the dendritic cells are severely impaired, thus limiting an efficient immune response on the other hand[59]. However, endothelium is the main target of EBV which exerts its toxicity by destroying endothelial cells, so inducing a severe hemorrhagic syndrome (Figure 4)[60]. What is the role of fibrinolysis in the pathogenesis of such a bleeding? Unfortunately,

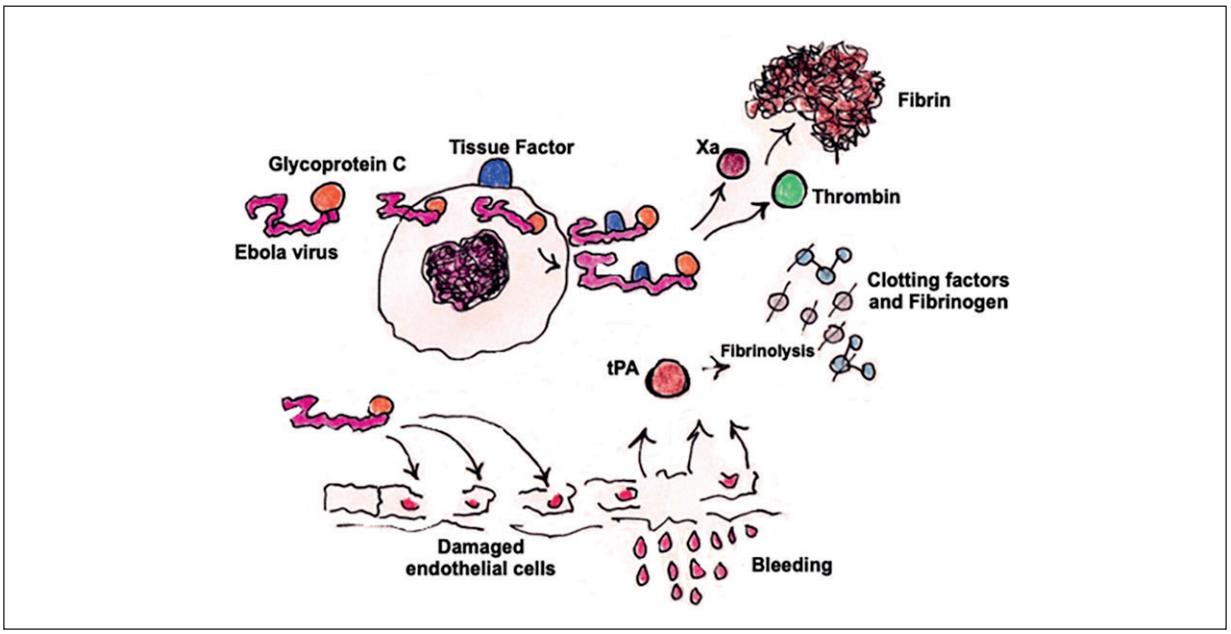


**Figure 4.** Virus (Dengue, Ebola) enter monocytes. After replication they carry TF exposed by these cells and their Glycoprotein C. Both activate blood coagulation. However, Ebola virus, but also Dengue virus, strongly attacks endothelial cells which result severely damaged. Fibrinolysis is thus greatly activated by the release of a large amount of t-PA. *Abbreviations:* t-PA Tissue Plasminogen Activator.

no reports on the behavior of fibrinolysis have been published because of safety reasons on one hand and the unavailable laboratory methods in the affected areas on the other. In a study carried out during the outbreak in Uganda in 2000, 123 positive patients were studied[61]. The concentration of D-Dimer was extremely high reaching values of ~520.000 ng/mL, in a fatal case 5 days after onset. Other non-fatal cases also showed very high levels of DD ranging from ~240.000 to 390.000 ng/ml. However, D-Dimer levels were 4 times higher in patients with fatal outcomes than in survivors (180,000 *vs.* 44,000 ng/mL), during the acute phase of the infection. The authors concluded that DIC was present in these patients, but no other test related to both blood coagulation and fibrinolysis was done. Again, in a small study on 5 patients with Ebola virus disease in Sierra Leone, higher PT, and D-dimer values were found in comparison with healthy controls[62].

## Discussion

As described, the behavior of different pathogens is functional to the virulence of infectious agents. It is interesting to note that the hemostatic and fibrinolytic systems are always involved but in a opposite way depending on the type of infectious agent. If nCoV-19, sepsis and plasmodium falciparum greatly exploit the activation of plasma clotting by inducing a condition of hypercoagulation supported by the inhibition of fibrinolysis, thus making the clot obtained stronger, others, such as YP and the infectious agents of the HF use the activation of fibrinolysis to perform their powerful lethality. It all depends on the target that the different infectious agents have. If infection by Gram-negative and Gram-positive bacteria induces an important inflammatory response by making blood clotting massively activated[63], nCoV-19 uses ACE2 receptors as a target. Since ACE2 receptors are widely distributed especially in the lung, the cause mortis is especially a respiratory failure where pulmonary thrombosis plays an essential role. It is the excess of individual response that leads to immuno-thrombosis, that is, the combined effect of innate immunity, especially supported by monocytes and cytokines, and coagulation activation supported by the inhibition of fibrinolysis that induces the disastrous effects of nCoV-19 infection[64]. Malaria infection is instead characterized by the pro-thrombotic role of erythrocytes which play a decisive role in inducing endothelial damage capable of transforming

these cells from anti-thrombotic to pro-thrombotic ones. The example of malaria is important because it highlights the role of erythrocytes in the pathophysiology of Hemostasis and Thrombosis, unfortunately very often ignored. The rheological properties of erythrocytes are in fact important because they contribute to fibrin-formation as they can expose phosphatidylserine which adsorb the coagulation factors ready to be used for fibrin formation[65]. This mechanism is important not only in the pathogenesis of malaria but may be crucial also in the nCoV-19 infection since a platelets-erythrocytes interaction has been detected in that infection so inducing erythrocytes aggregation functionally important in the microvasculature thrombotic occlusions of the disease[66]. Also, cytokines can attack erythrocytes so causing membrane damage, altering their structure, leading to immunologic clearance, or other vaso-occlusive mechanisms leading to thrombosis[67].

Finally, transfusion of red blood cells units predicted mortality in those admitted to the ICU as reported by Grandone et al[68] and strongly interacted with the admission to ICU (OR: 9.9; 95% CI: 2.5-40.0). As far as the therapeutic approach, either anti-thrombotic or anti-fibrinolytic drugs may have a role in the treatment of the infections described above. If we take into consideration the prothrombotic phenotype, it is known that in sepsis heparin has not shown to be effective, but it can be useful in reducing mortality in patients with sepsis and DIC[69]. Low molecular weight heparin (LMWH) prophylaxis failed in reducing the incidence of deep vein thrombosis especially in patients with nCoV-19 infection admitted to ICU[70]. Nevertheless, such a treatment has been found to reduce mortality[71]. It has been proven that both heparins and fondaparinux have both anti-viral and anti-inflammatory properties which may be crucial in contrasting the devasting activity of nCoV-19 but their administration, we believe, should be done earlier in the course of the disease, i.e., before the patients enter a ICU[72-74]. Otherwise, all the beneficial effects of these drugs would be inexorably missed. Recently, several trials have been interrupted since the effect of therapeutic doses of LMWH showed significantly more efficacy than the prophylactic regimen thus confirming that the use of a prophylactic dosage is to be avoided particularly in patients admitted to an ICU[75]. Even a thrombolytic treatment could be of value in the therapeutic approach to nCoV-19 infection with refractory acute respiratory distress syndrome, a possible algorithm has been proposed to consider such a treatment in this severe condition provided that no contraindication to systemic fibrinolysis does exist[76]. However, great caution is suggested before introducing this therapeutic regimen because no controlled data are available until now being this kind of treatment perhaps reserved to extremely severe nCoV-19 respiratory failure. Malaria is another disease which may deserve attention to a possible anticoagulant treatment since the prothrombotic burden is extremely great. In particular, heparin may be useful not only for its anticoagulant activity but also for its effect against the binding of Plasmodium Falciparum to erythrocytes[77]. Finally, anti-fibrinolytic drugs, such as tranexamic acid, could have a role in the infectious diseases characterized by a hemorrhagic phenotype.

## Conclusions

In this narrative review we tried to examine the peculiar features of different infectious disease characterized by an opposite involvement of the hemostatic system. It is worth noting that blood coagulation and fibrinolysis are greatly activated based on the strategy of the different infectious agents which exploit the excess of response of both systems to achieve the greatest possible virulence. These mechanisms are complex and require a proper knowledge in the thrombosis and hemostasis field. This concept is also of value in planning therapeutic interventions in the different infectious diseases where anti-thrombotic and anti-fibrinolytic drugs could be of help in contrasting the course of these diseases characterized by a high mortality rate.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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