Sepsis and Thrombosis

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Semin Thromb Hemost 2013;39:559–566.

Abstract

Activation of coagulation frequently occurs in severe infection and sepsis and may contribute to the development of thrombosis. Coagulation abnormalities in sepsis range from a small decrease in platelet count and subclinical prolongation of global clotting times to fulminant disseminated intravascular coagulation (DIC), characterized by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites. Septic patients with severe forms of DIC may present with manifest thromboembolic disease or clinically less apparent microvascular fibrin deposition, which predominantly presents as multiple organ dysfunction. Thrombophilia is associated with a prohemostatic state and consequently with an increased tendency to develop thrombosis. Hypothetically, patients with thrombophilia may suffer from more severe coagulopathy in case of severe infection or sepsis, which may result in a more serious clinical course and an unfavorable outcome. On the basis of the knowledge of the pathogenesis of thrombosis in severe inflammation and sepsis, strategies aimed at the inhibition of coagulation activation have been developed and have been found favorable in experimental and clinical studies.

Keywords
- sepsis
- thrombosis
- inflammation
- thrombophilia
- heparin

Sepsis is a clinical syndrome that is caused by an infection, often associated with bacteremia and characterized by the presence of systemic signs and symptoms of inflammation.[1] When sepsis leads to organ failure, the term severe sepsis is used. The incidence of sepsis is estimated to be approximately 2.5 per 1,000 in the Western world and shows a rapid 8.7% annual increase over the past 20 years.[2] Total in-hospital mortality of sepsis is around 20%, whereas severe sepsis is associated with mortality rates of 40 to 50%.[3] Treatment of sepsis is focused on adequate antibiotic therapy, source control, and appropriate supportive care and organ function replacement, if required.

Virtually all patients with sepsis have coagulation abnormalities. These abnormalities range from subtle activation of coagulation that can only be detected by sensitive markers for coagulation factor activation to somewhat more stronger coagulation activation that may be detectable by a small decrease in platelet count and subclinical prolongation of global clotting times to fulminant disseminated intravascular coagulation (DIC), characterized by simultaneous widespread microvascular thrombosis and profuse bleeding from various sites.[4,5] Septic patients with severe forms of DIC may present with manifest thromboembolic disease or clinically less apparent microvascular fibrin deposition, which predominantly presents as multiple organ dysfunction.[4,6,7] Alternatively, severe bleeding may be the leading symptom,[8] but quite often a patient with DIC has simultaneous thrombosis and bleeding. Bleeding is caused by consumption and subsequent exhaustion of coagulation proteins and platelets, due to the ongoing activation of the coagulation system.[9] In its

published online
April 27, 2013

Issue Theme Disease-Specific Thrombosis; Guest Editor, Marcel Levi, MD, PhD

DOI http://dx.doi.org/10.1055/s-0033-1343894.
ISSN 0094-6176.

most severe form, this combination may present as the Waterhouse–Friderichsen syndrome, commonly seen during fulminant meningococcal septicemia, although many other microorganisms may cause this clinical state.[10]

Relevance of Prothrombotic Changes in Patients with Sepsis

There is ample evidence that activation of coagulation in concert with inflammatory activation can result in microvascular thrombosis and thereby contributes to multiple organ failure in patients with severe sepsis.[11] First, extensive data have been reported on postmortem findings of patients with coagulation abnormalities and DIC in patients with severe infectious diseases.[12,13] These autopsy findings include diffuse bleeding at various sites, hemorrhagic necrosis of tissue, microthrombi in small blood vessels, and thrombi in midsized and larger arteries and veins. The demonstration of ischemia and necrosis was invariably due to fibrin deposition in small and midsized vessels of various organs.[14] Importantly, the presence of these intravascular thrombi appears to be clearly and specifically related to the clinical dysfunction of the organ. Second, experimental animal studies of DIC show fibrin deposition in various organs. Experimental bacteremia or endotoxemia causes intra- and extravascular fibrin deposition in kidneys, lungs, liver, brain, and various other organs. Amelioration of the hemostatic defect by various interventions in these experimental models appears to improve organ failure and, in some but not all cases, mortality.[15–18] Interestingly, some studies indicate that amelioration of the systemic coagulation activation will have a profound beneficial effect on resolution of local fibrin deposition and improvement of organ failure.[8,19] Finally, clinical studies support the notion of coagulation as an important denominator of clinical outcome. DIC has shown to be an independent predictor of organ failure and mortality in patients with sepsis.[6,20] In a consecutive series of patients with severe sepsis, the mortality of patients with DIC was 43%, as compared with 27% in those without DIC.[21] In this study, the severity of the coagulopathy was also directly related to mortality in septic patients.

Apart from microvascular thrombosis and organ dysfunction, coagulation abnormalities may also have other harmful consequences. The relevance of thrombocytopenia in patients with sepsis is in the first place related to an increased risk of bleeding. Indeed, in particular, critically ill patients with a platelet count of less than 50×10^9/L have a four- to fivefold higher risk for bleeding as compared with patients with a higher platelet count.[22,23] The risk of intracerebral bleeding in patients with sepsis during intensive care admission is relatively low (0.3 to 0.5%), but in 88% of patients with this complication, the platelet count is less than 100×10^9/L.[24] Regardless of the cause, thrombocytopenia is an independent predictor of intensive care unit (ICU) mortality in multivariate analyses with a relative risk of 1.9 to 4.2 in various studies.[22,23,25] In particular, a sustained thrombocytopenia during more than 4 days after ICU admission or a drop in platelet count of more than 50% during ICU stay is related to a four- to sixfold increase in mortality.[22,26] The platelet count was shown to be a stronger predictor for ICU mortality than composite scoring systems, such as the Acute Physiology and Chronic Health Evaluation II score or the Multiple Organ Dysfunction Score.

Prothrombotic Mechanisms in Sepsis

In recent years, the mechanisms involved in the pathological derangement of coagulation in patients with sepsis have become increasingly clear. Apparently, various mechanisms at different sites in the hemostatic balance act simultaneously toward a procoagulant state. It has become clear that the most important mediators that orchestrate this imbalance of the coagulation system during sepsis are cytokines.[5,27] Increasing evidence points to extensive cross-talk between these two systems, whereby inflammation leads to activation of coagulation and coagulation in turn considerably affects inflammatory activity.[28] Interestingly, systemic activation of coagulation and inflammation in sepsis can have some organ-specific manifestations, which are relevant for the specific organ dysfunction as a consequence of severe sepsis.[29]

It has become apparent that the principal initiator of thrombin generation in sepsis is tissue factor. The evidence that points to a pivotal role of the tissue factor/factor VIIa system in the initiation of thrombin generation comes from studies of human endotoxemia or cytokinemia, which did not show any change in markers for activation of the contact system.[30,31] Furthermore, abrogation of the tissue factor/factor VII(a) pathway by monoclonal antibodies specifically directed against tissue factor or factor VIIa activity resulted in a complete inhibition of thrombin generation in endotoxin-challenged chimpanzees and prevented the occurrence of DIC and mortality in baboons, which were infused with *Escherichia coli*.[17,32,33]

Platelets play a pivotal role in the pathogenesis of coagulation abnormalities in sepsis. Platelets can be activated directly, for example, by proinflammatory mediators, such as platelet-activating factor.[34] Once thrombin is formed, this will activate additional platelets. Activation of platelets may also accelerate fibrin formation by another mechanism. The expression of P-selectin on the platelet membrane not only mediates the adherence of platelets to leukocytes and endothelial cells but also enhances the expression of tissue factor on monocytes.[35] The molecular mechanism of this effect relies on nuclear factor kappa-B activation, induced by binding of activated platelets to neutrophils and mononuclear cells. P-selectin can be relatively easily shed from the surface of the platelet membrane, and soluble P-selectin levels have been shown to be increased during systemic inflammation.[35]

In general, activation of coagulation is regulated by three major anticoagulant pathways: antithrombin, the protein C system, and tissue factor pathway inhibitor (TFPI). During sepsis-induced activation of coagulation, the function of all three pathways can be impaired. Antithrombin is a serine protease inhibitor and the main inhibitor of thrombin and factor Xa. During severe inflammatory responses, antithrombin levels are markedly decreased because of consumption (as a result of ongoing thrombin generation), impaired synthesis (as a result of a negative acute phase response), and

degradation by elastase from activated neutrophils.[36,37] A reduction in glycosaminoglycan availability at the endothelial surface (due to the influence of proinflammatory cytokines on endothelial synthesis) will also contribute to reduced antithrombin function, since glycosaminoglycans act as physiological heparin-like cofactors of antithrombin. Binding of glycosaminoglycans to antithrombin induces a conformational change at the reactive center of the antithrombin molecule, thereby rendering this protease inhibitor from a slow to a very efficient inhibitor of thrombin and other active coagulation factors.[38] Prospective clinical studies in patients at high risk for sepsis have shown that a marked decrease in levels of antithrombin precedes the clinical manifestation of the infection, which may indicate that antithrombin is involved in the early stages of coagulation activation during sepsis.[39]

Endothelial dysfunction is even more important in the impairment of the protein C system during inflammation. Under physiologic conditions, protein C is activated by thrombin bound to the endothelial cell membrane-associated thrombomodulin. Thrombomodulin is a membrane protein with several domains, including a lectin-like domain, six epidermal growth factor (EGF)-like repeats, a transmembrane domain, and a short cytoplasmatic tail.[40] The binding of thrombin to thrombomodulin occurs at the site of the EGF repeats.[41] This binding not only results in an approximately 100-fold increase in the activation of protein C but also blocks the thrombin-mediated conversion of fibrinogen into fibrin and inhibits the binding of thrombin to other cellular receptors on platelets and inflammatory cells. In addition, thrombomodulin accelerates the activation of the plasma carboxypeptidase thrombin-activatable fibrinolysis inhibitor, an important inhibitor of fibrinolysis.[42] Activated protein C regulates coagulation activation by proteolytic cleavage of the essential cofactors Va and VIIIa. Binding of protein C to the endothelial protein C receptor results in a fivefold augmentation of the activation of protein C by the thrombomodulin–thrombin complex.[43] However, during severe inflammation, such as occurs in sepsis, in addition to low levels of protein C due to impaired synthesis[36] and degradation by neutrophil elastase (which has been described at least in vitro),[44] the protein C system is defective due to downregulation of thrombomodulin at the endothelial surface, mediated by the proinflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin 1β (IL-1β).[45] Observations in patients with severe gram-negative septicemia indeed confirmed the downregulation of thrombomodulin in vivo and impaired activation of protein C.[46] In this study, histological analysis of skin biopsies from patients with meningococcal sepsis showed decreased endothelial expression of thrombomodulin, both in vessels with and without thrombosis. Animal experiments of severe inflammation-induced coagulation activation convincingly show that compromising the protein C system results in increased morbidity and mortality, whereas restoring an adequate function of activated protein C (APC) improves survival and organ failure.[47] Interestingly, experiments in mice with a one-allele targeted deletion of the protein C gene (resulting in heterozygous protein C deficiency) have more severe DIC and organ dysfunction and a higher mortality than wild-type littermates.[48]

A third inhibitory mechanism of thrombin generation involves TFPI, the main inhibitor of the tissue factor–factor VIIa complex. TFPI is a complex multidomain Kunitz-type protease inhibitor, which binds to the tissue factor–factor VIIa complex and factor Xa.[49] The TFPI–factor Xa complex may bind to negatively charged membrane surfaces, which may increase the local concentration of TFPI at cellular sites and facilitate inhibition of membrane-bound tissue factor–factor VIIa complex. The role of TFPI in the regulation of inflammation-induced coagulation activation is not completely clear. Experiments showing that administration of recombinant TFPI (r-TFPI) (and thereby achieving higher than physiological plasma concentrations of TFPI) blocks inflammation-induced thrombin generation in humans and the observation that pharmacological doses of TFPI are capable of preventing mortality during systemic infection and inflammation suggest that high concentrations of TFPI are capable of importantly modulating tissue factor–mediated coagulation.[15,50] However, the endogenous concentration of TFPI is presumably insufficiently capable of regulating coagulation activation and downstream consequences during systemic inflammation, as has been confirmed in a clinical study of patients with sepsis.[51,52]

Thrombophilia As a Risk Factor in Sepsis

Because the prohemostatic state in severe infection and sepsis seems to be relevant for the pathogenesis of organ dysfunction and mortality, it may be hypothesized that even a mild preexistent prothrombotic state in patients—such as that caused by thrombophilia, for example, due to a factor V Leiden mutation—would aggravate the coagulation derangement during infection and sepsis and thereby affect outcome. Interestingly, experimental and clinical studies point to an interaction between a factor V Leiden mutation and the outcome of severe infection or sepsis, although the results are sometimes conflicting.[53] Congenital thrombophilia is mostly due to a genetic variation in a gene encoding a coagulation factor or—in general clinically less relevant—a fibrinolytic protein.[54] Such gene polymorphisms have been described for the coagulation factors such as prothrombin, factor V, fibrinogen, and factor XIII and for the coagulation inhibitors such as antithrombin, protein C, and protein S. In the latter case, these mutations cause a deficiency of these natural anticoagulant factors. In the fibrinolytic system, the most relevant polymorphism is the 4G/5G variation in the gene encoding plasminogen activator inhibitor type I (PAI-1). This polymorphism results in mildly elevated levels of PAI-1 and is related to an increased risk of myocardial infarction and ischemic stroke.

Anecdotal reports have indicated that the presence of congenital thrombophilia may exacerbate the coagulopathy associated with severe infection and may even result in purpura fulminans.[55–59] Indeed, various coagulation defects seem to be associated with an aggravated coagulation response to infectious agents or sepsis, although a systematic overview is missing.[60,61]

Experimental studies seem to confirm the hypothesis. Severe (congenital) protein C deficiency in mice results in thrombophilia as well as a proinflammatory phenotype with higher total white blood cell counts and higher basal IL-6 levels as compared with wild-type mice.[62] Further protein C deficiency was shown to affect endotoxemia in a mouse model. In these experiments, mice with a one allele targeted deletion of the protein C, resulting in heterozygous protein C deficiency,[63] were subjected to endotoxemia.[48] Mice with a heterozygous deficiency of protein C had more severe DIC, as evidenced by a greater decrease in fibrinogen level and a larger reduction in platelet count. Also thrombin–antithrombin complex levels were 3.4-fold higher in protein $C^{+/-}$ mice as compared with wild-type mice, and histologic examination showed more fibrin deposition in lungs and kidneys in these mice. Survival at 12 hours after the endotoxin injection was diminished in the protein $C^{+/-}$ group. Interestingly, protein $C^{+/-}$ mice had significantly higher levels of proinflammatory cytokines TNF-α, IL-6, and IL-1β, indicating an interaction between the protein C system and the inflammatory response. This latter observation is consistent with many other studies indicating cross-talk between effects of protein C on coagulation and inflammatory modulation.[64]

Factor V Leiden is another thrombophilic phenotype that has been extensively studied. In a clinical study in 259 children with meningococcal sepsis, factor V Leiden carriers had more profound coagulopathy and purpura fulminans, but their carrier status had no significant effect on survival.[65] Unfortunately, both experimental and clinical studies in sepsis have not shown unequivocal results regarding the presence of the factor V Leiden mutation so far. In one study, endotoxemic mice carrying a heterozygous factor V Leiden mutation had a surprisingly lower mortality (19%) compared with their wild-type controls (57%).[66] In these experiments, factor V Leiden mice produced more thrombin than normal controls, indicating a more profound activation of coagulation. In contrast, in another study of experimental pneumococcal pneumonia in mice, no major protective effect of the factor V Leiden mutation was seen.[67] Also, markers of coagulation activation, both systemically and in the bronchoalveolar compartment, were not different between factor V Leiden mice and wild-type littermates. Remarkably, homozygosity for the factor V Leiden mutation protected against lethality in mice that were treated with ceftriaxone. Also, factor V Leiden mice did not differ significantly in their response compared with wild-type mice in a model of septic peritonitis, as reflected by similar degrees of activation of coagulation, inflammation, organ dysfunction, and survival.[68] In another experimental study, the effect of the presence of one or two alleles of the factor V Leiden mutation was investigated in lethal H1N1 influenza.[69] Factor V Leiden mutation did not influence the procoagulant response, lung histopathology, or survival in this study. Finally, however, in a more subtle model of endotoxin-induced coagulation activation in humans, it was demonstrated that heterozygous carriers of factor V Leiden had a more pronounced increase in markers of thrombin generation and fibrinogen to fibrin conversion.[70] The authors also found an increase in fibrinolytic activity in factor V Leiden–affected individuals, which they attributed to the facilitating role of soluble fibrin for endogenous fibrinolysis.

Prospective studies on the incidence or outcome of severe infections and sepsis in patients with a prothrombotic polymorphism or coagulation inhibitor deficiency are not available. However, some case–control studies have reported on the prevalence of thrombophilic abnormalities in cohorts of patients with severe sepsis.

Clinical studies on the role of factor V Leiden in sepsis also show variable results. The presence of the factor V Leiden mutation was analyzed in large cohorts of patients with severe sepsis that had been included in intervention studies with recombinant human APC.[71,72] In this cohort of 3,894 patients, the prevalence of factor V Leiden heterozygosity was 3.9%, which is slightly higher than the predicted allelic frequency of 2.5%.[73] The 28-day mortality in those with factor V Leiden was not significantly different from the control population (19.3 vs. 26.2%, respectively; risk ratio, 0.74; 95% confidence interval [CI], 0.53 to 1.03). Moreover, there were no differences in the incidence of serious bleeding or thrombotic events between factor V Leiden carriers and non–factor V Leiden carriers. In another publication in which the data of only one of these two studies were presented, patients with a heterozygous factor V Leiden mutation were shown to have a lower mortality (13.9%) than those without this mutation (27.9%, $p = 0.013$).[66] There was no different effect of treatment with recombinant human APC between the two groups. In the Copenhagen City Heart study, 9,253 individuals were screened for the presence of the factor V Leiden mutation and followed for a period of more than 7 years to establish the risk of hospitalization for any infectious disease and the subsequent risk of progression of disease to death.[74] The relative risk of any infection in carriers of the factor V Leiden mutation was 1.08 (95% CI, 0.87 to 1.35) as compared with noncarriers (after adjustment for age, sex, smoking, alcohol consumption, income, and level of education). In contrast with the previously mentioned study, patients with the factor V Leiden mutation in this study had a higher risk of death from infection as compared with patients who did not have this mutation (adjusted relative risk, 4.41; 95% CI, 1.42 to 13.67). The same group of authors presented data from four case cohorts of patients with gram-negative sepsis or invasive pneumococcal disease or intensive care admission.[75] When they compared their 1,249 patients with matched controls, they found in an adjusted logistic regression analysis that factor V Leiden carriers had a higher risk of intensive care admission (odds ratio, 1.62; 95% CI, 1.08 to 2.42) and were at increased risk of death (relative risk, 1.78; 95% CI, 1.13 to 2.81) compared with controls.

Treatment of Thrombotic Complications in Sepsis

The keystone of the treatment of hemostatic abnormalities in patients with sepsis is the specific treatment of the sepsis by appropriate antibiotics and control of the infectious source. However, in many cases, additional supportive treatment,

aimed at circulatory and respiratory support and replacement of organ function, is required. Coagulation abnormalities may proceed, even after proper treatment has been initiated. Treatment of overt thrombotic complications in sepsis is not different from treatment in other clinical circumstances, although the bleeding risk of antithrombotic treatment may be higher.

In some cases, supportive measures to manage microvascular thrombosis as a result of the coagulopathy in sepsis may positively affect morbidity and mortality. Experimental studies have shown that heparin can at least partly inhibit the activation of coagulation in sepsis.[76] Uncontrolled case series in patients with sepsis and DIC have claimed to be successful. However, a beneficial effect of heparin on clinically important outcome events in patients with DIC has never been demonstrated in controlled clinical trials.[77] Also, the safety of heparin treatment is debatable in DIC patients who are prone to bleeding. Therapeutic doses of heparin are indicated in patients with clinically overt thromboembolism or extensive fibrin deposition, such as purpura fulminans or acral ischemia. Patients with sepsis may benefit from prophylaxis to prevent venous thromboembolism (VTE), which may not be achieved with standard low-dose subcutaneous heparin.[78]

Theoretically, the most logical anticoagulant agent to use in case of a severe sepsis-induced coagulopathy is directed against tissue factor activity. Potential agents include recombinant TFPI, inactivated factor VIIa, and recombinant NAPc2, a potent and specific inhibitor of the ternary complex between tissue factor–factor VIIa and factor Xa.[79] Phase II trials of r-TFPI in patients with sepsis showed promising results,[80] but a phase III trial did not show an overall survival benefit in patients who were treated with r-TFPI.[81]

Because antithrombin is one of the most important physiological inhibitors of coagulation, and on the basis of successful preclinical results, the use of antithrombin concentrates in patients with DIC has been studied relatively intensively. Most of the randomized controlled trials concern patients with sepsis, septic shock, or both. All trials show some beneficial effect in terms of improvement of laboratory parameters, shortening of the duration of DIC, or even improvement in organ function.[82] A large multicenter, randomized controlled trial to directly address this issue showed no significant reduction in mortality of patients with sepsis who were treated with antithrombin concentrate.[83] Interestingly, post hoc subgroup analyses indicated some benefit in patients who did not receive concomitant heparin and in those patients with the most severe coagulopathy, but this observation needs prospective validation.[84]

A beneficial effect of recombinant human APC was demonstrated in two randomized controlled trials. First, in a dose-ranging clinical trial, 131 patients with sepsis were enrolled.[85] A randomized controlled phase III trial of recombinant human APC in patients with severe sepsis was prematurely stopped because of efficacy in reducing mortality in these patients.[71] Interestingly, patients who had DIC according to international criteria benefited more from the therapy with APC than patients who did not have overt DIC.[21] However, meta-analyses of published literature concluded that the basis for treatment with APC, even in patients with a high disease severity, was not very strong. A recently completed placebo-controlled trial in patients with severe sepsis and septic shock was prematurely stopped due to the lack of any significant benefit of APC.[86] Subsequently, the manufacturer of APC has decided to withdraw the product from the market.

In a phase III randomized double-blind clinical trial in patients with DIC, administration of soluble thrombomodulin had a significantly better effect on bleeding manifestations and coagulation parameters than heparin, but the mortality rate at 28 days was similar in the two study groups.[87] When limiting these results to patients with severe infection and sepsis, DIC resolution rates were 67.5% in thrombomodulin-treated patients and 55.6% in the control group, and 28-day mortality rates were 21.4 and 31.6%, respectively. Mortality rates of patients who recovered from DIC were 3.7% in the thrombomodulin group and 15% in the heparin group.[88]

Prevention of Thrombosis in Sepsis

VTE is a common complication in critically ill patients. Reported rates for deep vein thrombosis in patients admitted to the ICU range from 22 to 80% depending on patient characteristics. Thromboprophylaxis with unfractionated or low-molecular-weight heparin (LMWH) lowers the risk for deep vein thrombosis by more than 50%.[89] Nevertheless, the risk of VTE in critically ill patients receiving (LMWH) heparin prophylaxis is still much higher than in other patient groups. Among several factors that may explain the higher incidence of VTE in critically ill patients, such as full immobilization or withholding anticoagulant prophylaxis because of a high bleeding risk, it was hypothesized that limited bioavailability (i.e., lower plasma antifactor Xa activity) of subcutaneously administered heparin in those patients with impaired peripheral circulation, due to vasopressor medication to maintain central blood pressure, might be important. Indeed, in a comparative trial, it was shown that critically ill patients on high-dose vasopressor medication had much lower antifactor Xa concentrations after the subcutaneous administration of LMWH in comparison with intensive care patients who had lower doses of vasopressor or in comparison with patients in the surgical ward.[90] A subsequent study also found consistently lower antifactor Xa levels after subcutaneous heparin in critically ill patients.[91] In another similar study, critically ill patients with excessive subcutaneous edema had lower antifactor Xa concentrations compared with a control group without edema.[92] This observation was confirmed in a group of critically ill multiple trauma patients, who showed variable and low heparin concentrations after subcutaneous injections.[93] The clinical relevance of lower antifactor Xa levels after conventional doses of (low-molecular-weight) heparin in critically ill patients is also not totally clear. Theoretically, the low antifactor Xa levels may lead to suboptimal prophylaxis and could indeed be a contributory factor to the higher incidence of thromboembolic complications in critically ill patients despite routine thromboprophylaxis. However, this has never been demonstrated in a clinical study. A

randomized controlled trial with conventional versus higher doses of thrombosis prophylaxis in critically ill patients aiming at reducing the incidence of VTE and other clinically relevant outcomes is justified. Such a study would also enable the evaluation of bleeding complications related to the administration of prophylactic heparin, as intensive care patients are at higher risk for hemorrhage as well.[94] A recent trial showed that the novel oral antifactor Xa anticoagulant rivaroxaban was noninferior to heparin in the prevention of VTE in critically ill medical patients.[95]

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