

# Coagulation Disorders and Hemostasis in Liver Disease: Pathophysiology and Critical Assessment of Current Management

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Normal coagulation has classically been conceptualized as a Y-shaped pathway, with distinct “intrinsic” and “extrinsic” components initiated by factor XII or factor VIIa/tissue factor, respectively, and converging in a “common” pathway at the level of the FXa/FVa (prothrombinase) complex. Until recently, the lack of an established alternative concept of hemostasis has meant that most physicians view the “cascade” as a model of physiology. This view has been reinforced by the fact that screening coagulation tests (APTT, prothrombin time – INR) are often used as though they are generally predictive of clinical bleeding. The shortcomings of this older model of normal coagulation are nowhere more apparent than in its clinical application to the complex coagulation disorders of acute and chronic liver disease. In this condition, the clotting cascade is heavily influenced by numerous currents and counter-currents resulting in a mixture of pro- and anticoagulant forces that are themselves further subject to change with altered physiological stress such as super-imposed infection or renal failure. This report represents a summary of a recent multidisciplinary symposium held in Charlottesville, VA. We present an overview of the coagulation system in liver disease with emphasis on the limitations of the current clinical paradigm and the need for a critical re-evaluation of the current tenets governing clinical practice. With the realization that there is often limited or conflicting data, we have attempted to represent diverse opinion and experience from the perspectives of both hepatology and hematology beginning with a brief update on the physiology of normal coagulation. (HEPATOLOGY 2006;44:1039-1046.)

Abbreviations: DIC, disseminated intravascular coagulopathy; PT, prothrombin time.

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Received January 18, 2006; accepted June 14, 2006.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.21303

Potential conflict of interest: Dr. Caldwell advises, is on the Speakers' Bureau for, and received grants from Novo Nordisk. Dr. Hoffman is a consultant and is on the Speakers' Bureau for Novo Nordisk. Dr. Lisman received grants from Novo Nordisk.

In spite of the prominence afforded to coagulation indices in the management of patients with liver disease (both in bleeding risk assessment and prognosis), relatively few clinical strides have been made recently in this field and many of the laboratory advances have not been translated into clinical practice. However, several developments have served to refocus attention on this subject. First, the development of recombinant activated factor VII (rFVIIa) has led to a much clearer understanding of the normal clotting cascade and to the possible role of this agent in treating the coagulopathy of liver disease.<sup>1-3</sup> Moreover, two important studies have raised serious questions about the clinical use of the prothrombin time (PT) and particularly the related International Normalized Ratio (INR) in both measuring liver disease prognosis and in estimating bleeding risk thus calling into question many common and traditional clinical practices.<sup>4,5</sup> This report represents a summary of a recent multidisciplinary symposium held in Charlottesville, VA, in which we critically reviewed this field. Our goals are to focus attention on areas of unmet need for clinical investigation and to foster critical thought about coagulation disorders in liver disease where the two fields of hematology and hepatology converge.

### **Modern Concepts of Normal Coagulation** (Maureane Hoffman, M.D., Ph.D.)

The cell-based model that integrates both the humoral cascade and cellular factors is now widely accepted as representative of actual hemostasis *in vivo*.<sup>6</sup> The process is initiated when cells bearing tissue factor (TF), a transmembrane protein that acts as a receptor and cofactor for FVII, are exposed at a site of injury. Subsequent (and simultaneous) events can be summarized as follows. The resulting FVIIa/TF complex catalyzes activation of FX and FIX. FXa then interacts with its cofactor Va to generate a small amount of thrombin. Simultaneously, FVIII bound to multimeric von Willebrand factor (vWF) and platelets bind to the extracellular matrix at the site of injury forming a platelet plug (primary hemostasis). This provides a phospholipid platform upon which the small amount of "priming" thrombin activates the bound platelets and other factors (FV, FVIII and FXI) that then amplify the process.

The platelet can thus be seen to perform two functions: primary hemostasis through formation of the vWF-platelet-collagen plug and service as a phospholipid platform which facilitates activity of the TF-FVIIa complex. Propagation of the clotting cascade is then achieved by a burst of thrombin on the platelet phospholipid membrane surface mediated by assembly of the "tenase" (FIXa/FVIIIa) complex and the "prothrombinase complex" (FXa and FVa) which results in formation of a sufficient amount of fibrin to form a meshwork and to stabilize the initial platelet plug. The overall

stability of the resulting clot depends subsequently on the activity of the innate thrombolytic system the components of which are further reviewed below.

Although each step of the cell-based model has been presented as an isolated set of reactions including initiation, amplification, and propagation, they should be viewed as an overlapping continuum of events. From this brief review it is evident that normal hemostasis depends on the complex interaction of several variables including coagulation factors, cellular tissue factor and platelet function. These interactions are not reflected in our commonly available coagulation tests.

### **Pathophysiology of Coagulation in Liver Disease: A (re) Balanced System?** (Ton Lisman, Ph.D.)

Bleeding is a common clinical problem in patients with liver disease. Although it is generally believed to result from an inherent hemostatic defect, this concept has recently been challenged as changes occur in both pro- and antihemostatic pathways such that the net result is often balanced in many respects. Moreover, life-threatening hemorrhage is often related more to portal hypertension than to net function of the clotting cascade (as in variceal hemorrhage). Nonetheless, there are major alterations in the hemostatic pathways in most patients with liver disease including altered platelet and endothelial function, altered clotting factors and conditions such as hyperfibrinolysis, dysfibrinogenemia and renal failure which may be superimposed on these underlying abnormalities.

Thrombocytopenia, usually from hypersplenism (and possibly from altered thrombopoietin metabolism or antiplatelet antibodies), is common in patients with cirrhosis. However, multiple mechanisms exist that alter platelet function both positively and negatively.<sup>7</sup> Increased production of two important endothelial-derived platelet inhibitors nitric oxide and prostacyclin, may contribute to defective platelet activation *in vivo*.<sup>8</sup> On the other hand, high plasma levels of vWF in cirrhosis appear to support platelet adhesion.<sup>9</sup> Reduced levels of coagulation factors V, VII, IX, X, XI, and prothrombin are also commonly observed in liver failure. In contrast, factor VIII levels are often elevated.<sup>10</sup> Vitamin K-dependent clotting factors (II, VII, IX, X) may be defective in function as a result of decreased  $\gamma$ -carboxylation (from vitamin K deficiency or intrinsically impaired carboxylase activity). Fibrinogen levels are found within the normal range in patients with stable disease, but decreased levels are found with more advanced cirrhosis and in patients with acute liver failure. Although debated as to significance, fibrinogen is

often functionally aberrant due to excessive sialic acid content (dysfibrinogenemia).<sup>11</sup> Endothelial dysfunction and vasodilation possibly mediated by endocannabinoids and nitric oxide, and altered sub-endothelial-platelet interaction further impairs hemostasis.<sup>12</sup> However, many of these changes are offset by decreased anticoagulant proteins such as protein C, protein S, protein Z, protein Z-dependent protease inhibitor, antithrombin, heparin cofactor II, and  $\alpha$ 2-macroglobulin, all of which are synthesized by the liver. Levels of tissue factor pathway inhibitor (TFPI) synthesized by endothelial cells are variably reported as normal or decreased in patients with liver failure.<sup>13</sup>

As with the clotting cascade, clot lysis (fibrinolysis) may be altered positively and negatively with a net result that there appears to often be a precarious balance between pro- and anti-fibrinolytic pathways. Reduced levels of plasminogen, antiplasmin ( $\alpha$ -2 plasmin inhibitor or  $\alpha$ -2 PI), thrombin activatable fibrinolysis inhibitor (TAFI), and factor XIII are reported in acute and chronic liver failure. On the other hand, plasma levels of tissue plasminogen activator (tPA) are elevated due to enhanced release by the activated endothelium and/or by reduced hepatic clearance. PAI-1 (plasminogen activator inhibitor, which blocks fibrinolysis) levels are also increased, but not to the same extent as tPA, except in acute liver failure, in which PAI-1 levels are substantially increased.<sup>14</sup> With the exception of patients with acute hepatic failure (wherein elevated PAI-1 levels may impair fibrinolysis), the net effect of these changes has been often described as "hyperfibrinolytic."<sup>15</sup> This remains controversial but there do appear to be patients with cirrhosis who have a bleeding diathesis due to an acquired state of hyperfibrinolysis (see below).<sup>16</sup>

Superimposed on these abnormalities are other conditions that can tilt the balance toward a net bleeding tendency. Renal failure is common in advancing liver disease. It usually imparts a bleeding risk due to acquired platelet dysfunction, abnormal platelet-vessel wall interaction, and anemia.<sup>17</sup> Another important and often coexisting problem is the occurrence of bacterial infections. A potential direct effect of endotoxin in activating the clotting cascade is suspected based on studies in normal individuals receiving intravenous tumor necrosis factor.<sup>18</sup> On the other hand, early studies suggest that endotoxin may inhibit coagulation by stimulating generation of an endogenous heparin-like substance in cirrhosis.<sup>19</sup> In addition, a relationship between endotoxin and prothrombin fragments has been reported and suggests that infection in cirrhosis contributes to the occurrence of the often-confusing "DIC-like" laboratory profile.

## **Hyperfibrinolysis versus DIC versus 'AICF' (Accelerated Intravascular Coagulation and Fibrinolysis)** (*B. Gail Macsik, M.D.*)

The literature regarding fibrinolysis and DIC in liver disease is complex and warrants some additional consideration. Reported laboratory abnormalities in cirrhosis include increased tPA and plasmin activity and decreased plasminogen,  $\alpha$ -2 plasmin inhibitor ( $\alpha$ -2 PI), and TAFI—key components in the process of fibrinolysis.<sup>20,21</sup> Although debatable, the extent of fibrinolysis is likely to be overestimated in patients with cirrhosis if the definition is based solely on these indirect markers instead of actual clot lysis measurements. For example, in one study, thromboelastography (TEG) failed to show evidence of fibrinolysis in 84 patients with decompensated cirrhosis.<sup>22</sup> However, a true hyperfibrinolytic state may develop when plasminogen activation by tPA is accelerated on the fibrin surface and decreased levels of  $\alpha$ -2 PI and PAI-1 fail to adequately control it. This clinically distinct situation, characterized by diffuse oozing from mucosal surfaces or bleeding from puncture wounds and delayed postprocedure bleeding, is relatively rare but requires recognition to facilitate appropriate therapy. Physiologic stress including infection may be key in tipping this process off through increased release of tPA.<sup>23</sup> The fibrinolytic properties of ascites fluid have also been implicated.<sup>24</sup>

Not uncommonly, laboratory abnormalities in decompensated cirrhosis come to resemble disseminated intravascular coagulation (DIC). Relatively stable platelet levels and characteristically high factor VIII levels distinguish this process from DIC as does the absence of uncompensated thrombin generation.<sup>25</sup> Moreover, classical end organ damage from intravascular coagulation is usually absent, although as noted below under hypercoagulation, subtle forms of microthrombotic disease may be relatively common. However, to account for the unusual features of both hyperfibrinolysis and DIC that are often evident in the decompensated liver disease patient, the term "accelerated intravascular coagulation and fibrinolysis" (AICF) has been proposed as a way to encapsulate the process under a single heading.<sup>26</sup> The essence of AICF can be postulated to be the result of formation of a fibrin clot that is more susceptible to plasmin degradation due to elevated levels of tPA coupled with inadequate release of PAI to control tPA and lack of  $\alpha$ -2 plasmin inhibitor to quench plasmin activity and the maintenance of high local concentrations of plasminogen on clot surfaces despite lower total plasminogen production. These normally balanced processes become pronounced when further disturbed by additional stress such as infection.

## Conventional Tests of Coagulation and Prognosis in Liver Disease (Arun Sanyal, M.D.)

Coagulation indices because of their relationship to liver synthetic function are well established as prognostic markers in a variety of settings in both acute and chronic liver disease.<sup>27,28</sup> Until just a few years ago, the long-standing Child-Pugh-Turcotte (CPT) score served as the basis for organ allocation for transplantation. Limitations in its range led recently to its replacement by the model end-stage liver disease (MELD) score the validity of which has been established in a number of studies.<sup>29</sup> Recent data have however tempered the enthusiasm over the use of the PT-INR as a component of the MELD score especially in regards to organ allocation. Trotter et al. demonstrated 26% variability in INR results when a sample of blood was sent to three reference laboratories resulting in a change in organ priority from the 58th to 77th percentile within their institution.<sup>4</sup> This marked variability in PT-INR results may reflect variability in the storage time, international sensitivity index (ISI) of the thromboplastin, the instrumentation, and/or the methodology used. It is not entirely surprising as this test was not developed nor standardized for use in patients other than those receiving vitamin K antagonists. On the basis of an extensive body of literature, these coagulation markers are clearly helpful in developing the prognosis, but the issue of test reproducibility has yet to be resolved.

## Conventional Tests of Coagulation and Bleeding Risk in Liver Disease (Armando Tripodi, Ph.D.)

Bleeding risk assessment is a well-established practice in the clinical evaluation of patients with liver disease. However, none of the commonly used tests have proven to be reliable. Among the oldest tests, the bleeding time (BT) is prolonged in cirrhosis and has been used to measure primary hemostasis and perhaps also reflects a deficit in the vasoconstrictor response.<sup>30,31</sup> In this regard, Boberg et al. reported that a prolonged BT was associated with a 5-fold increase risk of hemoglobin reduction after liver biopsy.<sup>32</sup> However, correction of the bleeding time has not correlated with decreased bleeding thus raising questions about the test's practical utility.<sup>33</sup> The platelet function analyzer (PFA-100) has been proposed as an alternative measure of platelet activity, but it has not been thoroughly investigated in patients with liver disease and its value in assessing the risk of bleeding is still uncertain.

Conventional tests of the clotting cascade such as the PT and APTT correlate poorly with procedure-related bleeding in patients with cirrhosis.<sup>34</sup> This lack of predic-

tive power can best be explained by deficiency of the naturally occurring anticoagulants protein C, antithrombin and TFPI that are reduced in parallel with procoagulant factors. Furthermore, protein C in vitro is activated poorly without thrombomodulin (absent in usual clinical assays) and therefore cannot exert its full anticoagulant activity. Thus, the balance of pro- and anticoagulants in platelet-free plasma from patients with cirrhosis is normal when assessed as thrombin generation in the presence of thrombomodulin in spite of prolongation of PT and APTT.<sup>5</sup> Further studies are underway to examine the role of the platelet in this process however it is now evident that the oft-cited (and usually arbitrary) preprocedure "cut-offs" for conventional coagulation indices (PT and PT-INR) lack a rational basis and need to be broadly reconsidered.

Specific tests of clot lysis or platelet aggregation are potentially useful in some clinical situations but limited by their availability. More global assays that take into account multiple variables including pro- and anticoagulation mechanisms and fibrinolysis warrant further study. Consistent with the potential utility of such assays, Boks et al. demonstrated a correlation between puncture wound and mucosal bleeding in hospitalized cirrhosis and acute liver failure patients using a composite score, which included a variant of the prothrombin time and an index of fibrinolysis.<sup>35</sup> Newer versions of the thromboelastogram (TEG) further offer automation and the ability to perform the test on citrated and recalcified blood for up to 3 hours after phlebotomy, thus greatly enhancing the practical utility of the test.<sup>36</sup> Key elements of the whole blood TEG include the reaction time ( $r$ ) which reflects the quantity of available factors, clot formation time ( $k$ ), the alpha angle ( $\alpha$ ) reflecting the rate of clot formation and indirectly indicating fibrinogen levels, the maximal amplitude ( $ma$ ) which is an indicator of platelet activity and finally a measure of clot lysis. Modifications of the primary assay, such as the addition of heparinase, make the test more robust but the dearth of clinical studies limit its application and endothelial function is not directly assessed in this assay.

## Prophylactic Versus Rescue Therapy in Approaching Bleeding Risk in Cirrhosis (K. Rajender Reddy, M.D., and Stephen H. Caldwell, M.D.)

The overall therapeutic strategy in approaching bleeding risk can be broadly divided into "prophylactic" or preventive therapy versus the wait and see approach of "rescue" therapy (i.e., intervention in the setting of active bleeding). The inherent clinical problem in either approach but especially with prophylactic therapy is the inadequacy of conventional laboratory tests to measure risk rather than an absence of risk. Since insistence on arbi-

**Table 1. Summary of Survey (n = 95)**

Respondents (%)	Primary role (%)	INR Predicts Postprocedure Bleeding	Threshold Platelets for Liver Biopsy	Threshold Platelets for ICP Monitor
GI-Hepatology (59)	Clinical MD (82)	Strongly agree (0)	<25,000 (4)	<25,000 (20)
Hematology (11)	Research (3)	Agree (21)	<30,000 (81)	<30,000 (46)
Blood Bank (14)	Non-MD HCP (13)	Don't know (8)	<50,000 (14)	<50,000 (34)
Surgery-Anesthesiology (10)	Pharmacology (5)	Disagree (58)	<100,000 (0)	<100,000 (0)
ICU (3)		Disagree strongly (13)		
Radiology (3)				

Renal failure adds to bleeding risk	FFP is effective in preventing bleeding	Transfusion reaction frequency	Basis of treatment decisions	Legal concerns after treatment
Strongly agree (35)	No effect (22)	Extremely common (0)	Clinical trials (8)	Strongly agree (6)
Agree (51)	Prevents some (49)	Quite common (45)	Expert opinion (32)	Agree (66)
Don't know (6)	Don't know (16)	Don't know (11)	Society guidelines (24)	Don't know (17)
Disagree (8)	Prevents most (14)	Uncommon (42)	Facility policy (19)	Disagree (9)
Strongly disagree (0)	Prevents all (0)	Very rare (3)	Conventional Rx (16)	Strongly disagree (3)

rary target indices may delay care and increase the risk of adverse events (infections and reactions to blood products for example) and even the risk of bleeding (portal pressure elevation from excessive volume expansion with plasma), only very cautious use of prophylactic therapy is warranted in the absence of valid end points.

We recently conducted an informal poll to assess the degree of variation in practice in the assessment of bleeding risk in patients with liver disease and the use of conventional laboratory tests. Questionnaires were completed by 95 participants in the Coagulation in Liver Disease symposium held in Charlottesville, VA, in October 2005. Some of these results are summarized in Table 1. Among the salient findings was the lack of confidence in standard measures of coagulation (such as the PT-INR) and the differences in approaches to procedures depending on the perceived relative risk (*i.e.*, liver biopsy versus intracranial pressure monitor placement). Fifty eight percent of the respondents indicated that PT-INR was not a good predictor of the risk of procedure related bleeding. Yet, 50% indicated that they would pursue a prophylactic strategy for a liver biopsy if the PT INR was >1.5, and 81% would use platelets for a count below 30,000/mm<sup>3</sup> prior to a liver biopsy. Little agreement existed for the threshold for use of a prophylactic strategy in placement of an intracranial pressure monitoring device: 55% and 34% indicated cutoffs of INR >1.5 and a platelet count of >50,000/mm<sup>3</sup>, respectively. The parameters for prophylactic use of FFP or other products, and platelets in situations of dialysis catheter placement where comparable to the responses elicited for liver biopsy. The majority felt that renal failure in patients with cirrhosis was associated with greater risk of bleeding. Of interest were the responses with regard to paracentesis, wherein close to 50% indicated that they either never use prophylaxis or

use it only if the INR was >2.5. For thoracentesis, the responses were even more heterogeneous.

Most responses were based on expert opinion or society guidelines. In spite of the acknowledged absence of sound data, many of the opinions were influenced by legal considerations. Although these results cannot be construed as treatment recommendations, they nevertheless constitute an informed opinion that calls for the need for the study of new end points to allow a more rational strategy in this field. Consideration of "PT correction" should be carefully weighed against the risk of the procedure and the potential side effects of the prophylactic intervention. In this regard, close to half of the respondents felt that adverse events related to blood products transfusions were quite common. Side effects such as TRALI (transfusion related acute lung injury) may go unrecognized in these often critically ill patients.<sup>37</sup>

### Therapeutic Agents (Stephen H. Caldwell, M.D.)

It should be recalled that portal hypertension, endothelial dysfunction (reduced vascular tone), bacterial infection and renal failure underlie a part of the bleeding diathesis in patients with liver disease. Thus measures to reduce portal hypertension, restore endothelial tone, resolve infection and to improve renal function should be considered as at least adjunctive measures in addressing active bleeding and bleeding risk. Conversely, therapy should avoid excessive volume expansion, which may exacerbate portal hypertension.

Specific agents include oral or parenteral vitamin K, which should be given if deficiency is suspected (especially with cholestasis, malnutrition or antibiotic therapy). Blood product use (platelets, plasma, and cryoprecipitate) should be tempered by their undefined efficacy, attendant

volume expansion, risk of infection, and costs (including hidden costs such as typing and screening, occasional pre-medication use, infusion-monitoring setups, and side effects such as pulmonary edema). Target platelet levels remain poorly defined but may be especially important given the dual effect of platelets in primary hemostasis (platelet plug) and as the major source of phospholipid that participates in generation of the thrombin burst.

The use of newer hemostatic agents must be tailored to the clinical situation and, to the extent possible, definition of specific coagulation disorders (i.e., thrombocytopenia, hypofibrinogenemia, hyperfibrinolysis). Recombinant activated factor VII (rFVIIa) offers the advantage of augmentation of the physiological “thrombin burst” at a site of vascular breach (where TF is exposed), enhanced activation of platelets in thrombocytopenia and renal failure and absence of volume expansion.<sup>2,38,39</sup> Single doses decrease clotting time in patients with cirrhosis without changing clot lysis time indicating formation of a viable clot. The half-life is about 2 hours and the duration of measurable effects is about 3–4 hours or more depending on the dose. Based on its mechanism of action, it may have its greatest role as a rescue agent or in very high-risk procedures such as intracranial pressure monitor placement. Its use is tempered by the high costs and an associated risk of potentially serious thrombotic disease estimated at 1% to 2%.<sup>40</sup> Antifibrinolytic agents, such as  $\epsilon$ -aminocaproic acid (EACA) and tranexamic acid (TA) are derivatives of lysine that inhibit plasmin. Aprotinin is a bovine-derived serine protease inhibitor that leads indirectly to diminution of fibrinolysis. These agents play a potentially significant role in treating well-defined hyperfibrinolysis (and as topicals in oral bleeding following dental extractions) but also carry a risk of thrombotic complications.<sup>41</sup> Desmopressin (DDAVP, 1-deamino-8-D-arginine vasopressin) is an analogue of the antidiuretic hormone vasopressin, which increases endogenous secretion of vWF and FVIII (see also above). Surprisingly, in light of the already elevated levels of vWF and factor VIII in cirrhosis, the agent shortens bleeding time in this situation (see above). In spite of this, clinical trials in cirrhosis have been disappointing.

The relative benefit of a specific intervention (i.e., plasma or rFVIIa) prior to a specific procedure depends on assessment of the relative risk of bleeding, the risk and costs of the intervention and the ease of management of a bleeding complication or treatment side effect should either occur. Based on current practice, average charges, and published risks, Hernandez and Northup performed a cost-efficacy analysis demonstrating that in patients undergoing liver biopsy, taking the approach of rescue intervention (should bleeding occur) using newer and

substantially more expensive agents such as rFVIIa is both safer and overall less expensive than conventional plasma-based prophylactic strategies.<sup>42</sup> Obviously, these data are based on many assumptions but their results reinforce the concept that an overall re-evaluation of conventional prophylactic measures is warranted both from a clinical point of view and based on efficient use of resources.

## Hypercoagulation in Liver Disease (Patrick Northup, M.D.)

An overview of coagulation disorders in liver disease would be incomplete without at least a brief discussion of the often-overlooked aspect of hypercoagulability in these patients. As noted above, “coagulopathy” as defined by the PT and PT-INR does not indicate “auto-anticoagulation” and should not be construed as protective from a hypercoagulable state.<sup>43</sup> Aside from decreased activity of the anticoagulant pathways, diminished flow as a result of stasis as well as disordered fibrinolysis may actually promote venous thrombosis.<sup>44,45</sup> Altered platelet phospholipid membrane activity could also contribute to this but remains to be established or refuted as a mechanism. However, it remains that peripheral deep vein thrombosis (DVT) and pulmonary embolism (PE) occur in patients with cirrhosis by an incidence of 0.5% to 1.0% for DVT or PE.<sup>46</sup> It is also known that patients with liver disease may manifest hypercoagulable states such as factor V Leiden deficiency and prothrombin G20210A mutations, methylenetetrahydrofolate reductase C677T mutation or the antiphospholipid antibody syndrome.<sup>47,48</sup>

Occult thrombotic processes may also be a factor in progression of stable cirrhosis to decompensated hepatic atrophy (parenchymal extinction) and pulmonary microthrombosis has also been implicated as a possible mechanism in the pathogenesis of the less frequent patient with portopulmonary hypertension.<sup>49,50</sup> Thus, hypercoagulation in cirrhosis may become manifest both in classical terms as with DVT or in far more subtle ways as with the proposed vasculopathies of parenchymal extinction and possibly portopulmonary hypertension. Optimal assessment and management of these issues remains to be defined.

## Summary and Future Goals (Stephen H. Caldwell, M.D., and Arun J. Sanyal, M.D.)

Normal hemostasis and coagulation is now viewed as primarily a cell-based process wherein key steps in the classical clotting cascade occur on the phospholipid membrane surface of cells (especially platelets) beginning with activation of tissue factor and factor VII at the site of vascular breach which produces an initial “priming”

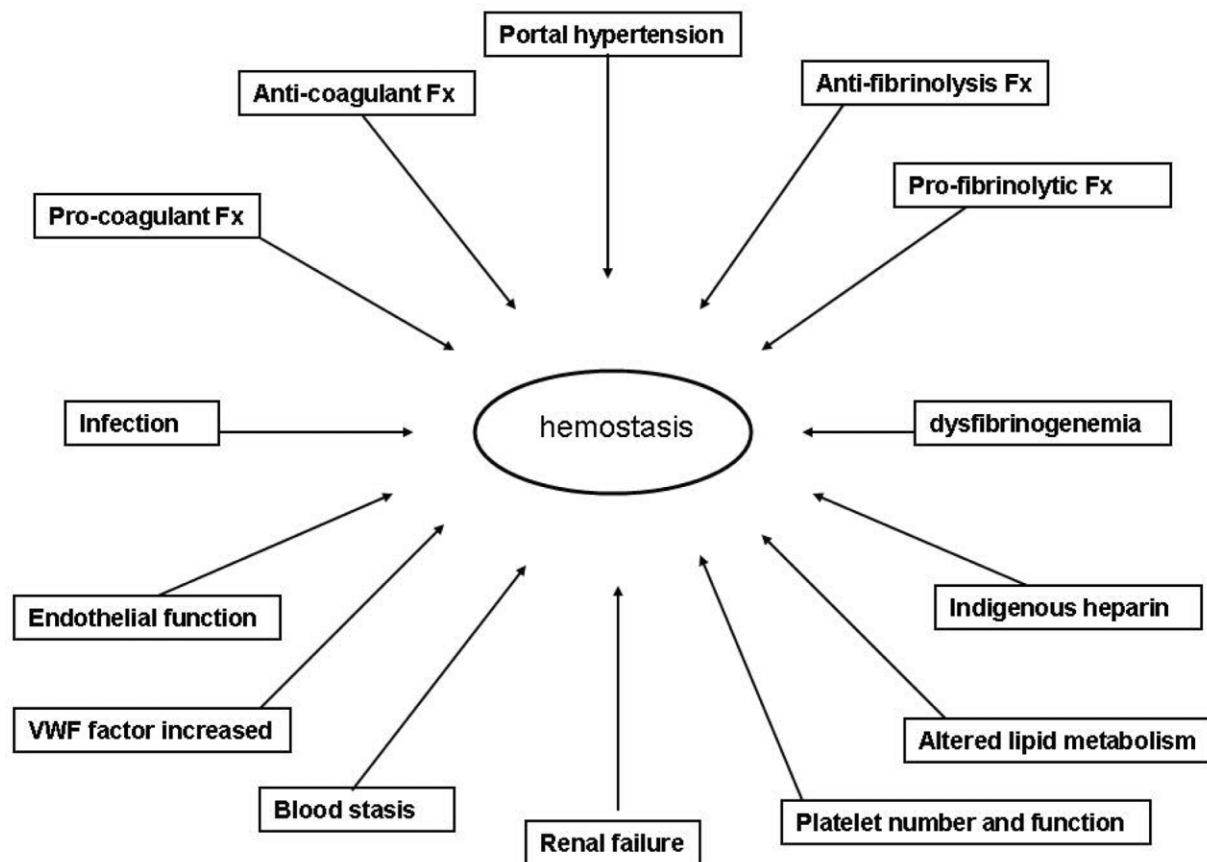


Fig. 1. Multiple interacting and often opposing variables converge to produce net hemostasis in the patient with liver disease.

amount of thrombin and a subsequent thrombin burst. Coagulation and hemostasis in the liver failure patient is influenced by multiple, often opposing, and sometimes changing variables and may even produce a hypercoagulable state (Fig. 1). Although a bleeding diathesis is usually predominant, the assessment of bleeding risk based on conventional laboratory tests such as the PT or PT INR is inherently deficient due to simultaneous impairment of the anticoagulation pathways. Whereas the PT and PT-INR are well established in measuring prognosis (albeit with yet to be resolved interlaboratory variation), their limitations in bleeding risk prediction necessitate caution in the prophylactic use of plasma and other procoagulant factors based on arbitrary “cutoff” values that lack sound physiological and clinical supportive evidence.

The decision to use prophylactic therapy should take into account the predominant underlying physiology, the history of bleeding and the risk-benefit of the procedure as well as the likelihood that rescue therapy would be available should bleeding occur. Further studies are clearly essential to learn how best to measure the net activity of the coagulation cascade in a given patient in order to make best use of the available options. Only then can the clinician determine whether to use blood factor replacement,

platelet augmentation or thrombin burst enhancement with rFVIIa, or to use antifibrinolytics based on the clinical situation. Until then, the authors recommend challenging unfounded dogma and to the extent that is possible, tailoring therapy to the individual situation.

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