Coagulopathy of Liver Disease

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Opinion statement

- Coagulopathy in patients with liver disease results from impairments in the clotting and fibrinolytic systems, as well as from reduced number and function of platelets.
- Parenteral vitamin K replacement corrects coagulopathy related to biliary obstruction, bacterial overgrowth, or malnutrition. Vitamin K is less effective for coagulopathy caused by severe parenchymal liver injury.
- Transfusion of fresh frozen plasma is the hallmark of treatment of significant coagulopathy in patients with liver disease and active bleeding.
- Transfusion of fresh frozen plasma also reverses moderate to severe coagulopathy of cirrhosis prior to invasive procedures.
- Cryoprecipitate is useful for severe coagulopathy with hypofibrinogenemia, especially when avoidance of volume overload is desired.
- Exchange plasmapheresis is useful in selected patients with coagulopathy due to liver disease, in whom fresh frozen plasma fails to correct coagulopathy or in patients who have coexistent severe fluid overload.
- Platelet transfusions, pooled or single donor, are useful in thrombocytopenic patients prior to performing invasive procedures or in the presence of significant bleeding, especially when the platelet count is below 50,000/mL.
- The use of recombinant factor VIIa and thrombopoietin therapy for correction of coagulopathy and thrombocytopenia, respectively, in patients with cirrhosis, is currently under investigation.
- Therapy with prothrombin complex concentrates, 1-deamino-8-D-arginine vasopressin and antithrombin III concentrates for the management of coagulopathy caused by liver disease can be hazardous and the use of these products is considered investigational at the present time.

Introduction

The physiology of blood coagulation is closely linked to liver function: the liver synthesizes most of the factors of the coagulation cascade and fibrinolytic proteins. In addition, the liver is intimately involved in the regulation of coagulation by facilitating the clearance of activated clotting and fibrinolytic factors, and activation complexes. A variety of hemostatic abnormalities occur in patients with liver disease and, in general, the severity of these abnormalities reflects the degree of hepatic dysfunction [1,2•]. Liver disorders can be associated with impaired synthesis of coagulation factors, production of abnormally functioning clotting factors (dysfibrinogenemia), vitamin K deficiency, impaired posttranslational modification of vitamin K–dependent clotting factors, thrombocytopenia, qualitative platelet dysfunction, consumptive coagulopathy (disseminated intravascular coagulopathy [DIC]) and impaired clearance of circulating activation complexes [1,3••]. In moderate to severe hepatocellular injury, functional assays of most procoagulants show decreases to about 50% to 70% of normal levels. Only in fulminant hepatitis or decompensated cirrhosis is the degree of synthetic failure generally sufficient to be a primary cause of bleeding.

Thrombocytopenia is a common consequence of portal hypertension, with up to 90% of the platelet pool being sequestered in the spleen (hypersplenism). Platelet counts between 30,000 to 40,000/mm^3 are often observed in patients with established cirrhosis, although serious spontaneous bleeding is uncommon. In advanced parenchymal liver disease, more severe qualitative and quantitative platelet abnormalities may be seen. The results of platelet function studies vary considerably and do not necessarily predict bleeding tendency [4•,5,6].

Both quantitative and qualitative abnormalities in coagulation factors can be seen. The hepatic synthesis of prothrombin and factors VII, IX, and X, protein C, and protein S includes vitamin K–dependent biochemical steps, such as gamma carboxylation [7]. The levels of these factors are often reduced in hepatocellular disease and, in general, the degree of reduction correlates with the severity of the liver disease. Factor VII level frequently is the first to diminish due to its short half-life, and hence serves as an important early marker of significant liver disease. Factor V level is reduced in acute and chronic liver disease. In contrast, factor VIII level may be normal even in the presence of advanced liver disease. The comparison of factor VIII with liver synthesized factors is often the only differentiating factor between the coagulopathy of liver failure and DIC when factor VIII levels typically are reduced.

Disseminated intravascular coagulopathy presents a diagnostic and therapeutic challenge in the patient with liver disease. Various theories propose liver necrosis and impaired endotoxin clearance as probable trigger events for development of DIC in liver disease. The coagulation profile in DIC is virtually indistinguishable from that seen in advanced liver disease, and unfortunately therapeutic options for this type of DIC are very limited [3••,8].

Primary activation of the fibrinolytic system may occur due to decreased production of tissue plasminogen activator inhibitor and reduced clearance of tissue plasminogen activator and alpha-2 antiplasmin by a diseased liver. This combination leads to a hyperfibrinolytic state that can result in catastrophic bleeding episodes [2•,9••,10].

COAGULOPATHY PATTERNS SEEN IN FREQUENT SYNDROMES OF LIVER DISEASE

Although overt bleeding is unusual (except in fulminant hepatitis or massive hepatic necrosis), in acute hepatitis (viral or toxic) laboratory abnormalities are common, including thrombocytopenia and mild to moderate prolongation of the prothrombin time. In chronic active hepatitis, significant bleeding is also uncommon due to sufficient residual mass of hepatocytes. However, prolongation of the prothrombin time is correlated with progression to cirrhosis, or with a severe flare-up or exacerbation of the necroinflammatory process. In cirrhosis, various degrees of thrombocytopenia, coagulation abnormalities, DIC, and impaired fibrinolysis often are present. In patients with decompensated and end-stage disease (those with ascites, hepatic encephalopathy, or severe portal hypertension), the prothrombin time may be very prolonged and platelet counts may reach nadirs of 30,000 to 40,000/cm^3. A very prolonged prothrombin time and progressive hypofibrinogenemia (lower than 100 mg/dL) are adverse prognostic signs that predate overt liver failure.

Treatment

Diet and lifestyle

- Nutritional deficiencies worsen coagulopathy. Specifically, vitamin K deficiency with deficient clotting factors and folate deficiencies with associated thrombocytopene are common in patients with biliary tract disease (obstructive jaundice, biliary cirrhosis) or prolonged fasting, respectively. These deficiencies can be corrected with daily exogenous supplementation of vitamin K, 10 mg subcutaneously, and folic acid, 1 mg orally or intravenously. The intravenous route for vitamin K should be avoided for due to the risk of anaphylaxis, angina, hypotension, cerebral vascular thrombosis, and even death [1,4•].
- Alcohol is directly toxic to platelets and bone marrow [11]. This effect is more pronounced in patients with cirrhosis, when hypersplenism and folate deficiency may be coexistent [11]. Hence, alcohol abstinence is essential in patients with liver disease and may result in qualitative and quantitative improvement in platelet function, thus improving hemostasis.

Pharmacologic treatment

- Due to the pivotal role of vitamin K in the hepatic synthesis of many coagulation factors, pharmacologic supplementation of this vitamin is a logical initial step toward correcting coagulopathy.
- In addition, support with various blood products is usually necessary when coagulopathy is severe or when significant bleeding ensues. Prophylactic use of blood products often is advocated prior to invasive procedures (*eg,* major surgical procedures, liver biopsy, multiple dental extractions, angiography) in patients with significant liver-dysfunction–related coagulopathy or severe thrombocytopenia.
- Recently, considerable interest has been generated regarding the use of recombinant factor VIIa and thrombopoietin in the correction of coagulopathy and thrombocytopenia associated with liver disease [12•,13]. However, their efficacy in clinical practice remains to be documented, and currently their use should be considered investigational.

Vitamin K

Standard dosage	2 to 10 mg/d of vitamin K (Aquamephyton; Merck and Co., Whitehouse Station, NJ) subcutaneously for three to five days until maximal correction of prothrombin time is obtained. Avoid the intravenous route due to risk of anaphylaxis and hypotension.
Contraindications	Known hypersensitivity. Patients with glucose-6-phospate dehydrogenase deficiency and newborns may develop hemolysis and kernicterus, respectively.
Main drug interactions	Vitamin K antagonizes the effect of warfarin.
Main side effects	Intravenous administration may produce flushing, chest pain, anaphylaxis, hypotension, and even death.
Special points	Onset of action is within 6 to 12 hours; full onset of effect is at 24 hours, lasting up to 7 days. Oral route not effective in biliary obstruction or biliary cirrhosis. The therapeutic effect of vitamin K is limited in the presence of hepatocellular disease. Store away from light.
Cost/cost-effectiveness	Inexpensive: about $5.00 per dose.

Transfusions of fresh frozen plasma

Standard dosage	Administer 10 to 15 mL/kg every 12 hours; measure prothrombin time a few hours after the transfusion. For invasive procedures and major surgery, the goal is to correct prothrombin time within 3 seconds of control.
Contraindications	Preexisting volume overload; known immunoglobulin-A deficiency.
Main drug interactions	None.
Main side effects	Risk of transfusion-transmitted infection with one unit of fresh frozen plasma is equivalent to that of transfused blood (*eg,* 1 in 600,000 risk of transmitting HIV). Adverse transfusion reactions may occur with a frequency of 1% to 6%.
Special points	Transfusion of fresh frozen plasma is a useful method for correction of significant coagulopathy due to liver disease. Monitor volume status of patient closely, especially when repeated fresh frozen plasma transfusions are used. Improvement in coagulopathy is transient, generally lasting 24 to 36 hours.
Cost/cost-effectiveness	Moderately expensive: $50 to $100 per unit, depending on the institution and processing charges.

Platelet transfusion

Standard dosage	Single-donor or pooled platelet transfusion; an optimal response to each unit transfused is a rise in platelet count by 10,000/mm^3; however, in practice, this degree of response may not be observed due to platelet sequestration.
Contraindications	Known hypersensitivity to blood products.

Main drug interactions	None.
Main side effects	Risk of transmission of infections and adverse transfusion reactions exists.
Special points	Prophylactic transfusion of platelets should be as close to the procedure as possible due to short half-life of platelets and rapid splenic pooling.
Cost/cost-effectiveness	Moderately expensive: about $50.00 for 4-unit bag.

Cryoprecipitate infusion

Standard dosage	1 to 4 units of cryoprecipitate (each unit contains about 150 to 200 mg of fibrinogen) per 10 kg body weight transfused, to maintain fibrinogen levels more than 100 mg/dL.
Contraindications	Known hypersensitivity.
Main side effects	Risk of transmission of infections and risk of adverse transfusion reactions exists.
Special points	Cryoprecipitate is produced by thawing fresh frozen plasma at 4 ºC. Should be transfused if fibrinogen level is less than 100 mg/dL. Useful in congenital and acquired hypofibrinogenemia and when volume overload is a concern.
Cost/cost-effectiveness	Relatively inexpensive: about $35 per bag.

Plasma exchange (plasmapheresis)

	Plasmapheresis is the isovolumetric replacement of patient's plasma by fresh frozen plasma.
Standard dosage	30 to 50 mL/kg of plasma is exchanged in a single session.
Contraindications	Hemodynamic instability. Known immunoglobulin-A deficiency.
Main drug interactions	None
Main side effects	Same as transfusions of fresh frozen plasma. In addition, symptomatic hypocalcemia may develop during the procedure, requiring prompt parenteral calcium administration.
Special points	Plasma exchange is useful to correct severe coagulopathy associated with liver disease, especially in cases where coagulopathy is resistant to treatment with standard fresh frozen plasma transfusions. Volume overload is not an issue with this isovolumetric procedure. With modern plasma exchanger machines, the procedure takes only 1 to 2 hours, achieving correction of coagulopathy much faster than standard transfusions of fresh frozen plasma. Due to large amounts of citrated plasma, the prothrombin time may show little or no improvement if measured immediately after the procedure until the excess citrate is metabolized.
Cost/cost effectiveness	Relatively expensive: approximate charges per in-patient procedure is $1200; cost of fresh frozen plasma used for replacement (about $1000 to $1500) also should be included.

1-deamino-8-D-arginine vasopressin infusion

Standard dosage	0.3 μg/kg 1-deamino-8-D-arginine vasopressin infusion (DDAVP; Rhone Poulenc, Rorer, Germany).
Contraindications	Patients with ischemic heart disease and cardiac arrhythmias, seizure disorders, hypersensitivity to vasopressin.
Main drug Interactions	Lithium, demeclocycline, and heparin decrease the effect. Chlorpropamide and phenformin potentiate effect.
Main side effects	1% to 10% incidence. Serious effects include bradycardia, angina, arrhythmias, venous thrombosis. Other adverse effects like fever, nausea and vomiting, tremor, and abdominal cramps may be seen.
Special points	May transiently shorten bleeding time in patients with liver disease. Utility and clinical benefit are uncertain.
Cost/cost-effectiveness	Relatively inexpensive.

Surgery

Liver transplantation

	Severe coagulopathy is the end result of advanced liver disease and liver failure. Successful liver transplantation restores hemostatic function.
Standard procedure	Total recipient hepatectomy and orthotopic implantation of the donor liver allograft.
Contraindications	AIDS, extrahepatic malignancy, active alcohol or substance abuse, severe cardiopulmonary risk factors.
Complications	Graft nonfunction, allograft rejection, increased risk of infections, hypertension, diabetes mellitus, and development of malignancies.
Special points	Coagulopathy (prothrombin time in seconds) contributes to Child's Pugh scoring system and the degree and rate of progression of coagulopathy is a useful guide in determining the need and urgency for liver transplantation.
Cost/cost-effectiveness	Expensive: cost of life-long follow-up and immunosuppression is a significant burden.

References and Recommended Reading

Recently published papers of particular interest have been highlighted as:
- • Of importance
- •• Of major importance

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