Routine Use of Vitamin K in the Treatment of Cirrhosis-Related Coagulopathy: Is it A-O-K? Maybe Not, We Say

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ABSTRACT

Historically, coagulopathy related to cirrhosis has been managed primarily as a bleeding disorder. However, several recent studies have shown that patients with cirrhosis have an increased risk of both bleeding and clotting. These coagulopathic changes are a result of the decreased synthetic capabilities of the cirrhotic liver. Vitamin K is often given to correct prolonged prothrombin times (PT) in patients with cirrhosis. However, this practice is not well defined and its effectiveness is questionable. The objective of our literature review is to determine the effectiveness of vitamin K to correct coagulopathy in cirrhosis. This report evaluates data published between 1981 and 2017. Published articles relevant to vitamin K use in cirrhotic patients were reviewed and summarized. The available literature regarding the use of vitamin K in cirrhosis is limited, and the research published so far does not appear to support its use. The routine uses of vitamin K to correct PT/international normalized ratio in hepatic cirrhosis should be avoided unless further studies can demonstrate true clinical benefit.

Keywords: hepatology, cirrhosis, liver, clinical pharmacology, phytonadione, vitamin K

INTRODUCTION

In the not-too-distant past, discussions about impaired hemostasis related to cirrhosis have focused on the proclivity for increased bleeding risk.1 However, more recent literature has recharacterized this concept, concluding that cirrhosis leads to a coagulopathic state whereby there is an increased risk of both bleeding and thrombosis.1-5 This coagulopathic imbalance is the result of several pathophysiologic changes that occur in cirrhosis, including a reduced rate of synthesis of coagulation factors by the cirrhotic liver. In cirrhosis, all procoagulant factors are decreased except for factor VIII and von Willebrand factor, which are actually increased because of reduced hepatic clearance. Also, the body’s natural anticoagulants, proteins C and S, are both reduced, which increases the likelihood of thrombotic events. As a result of these hemostatic imbalances, patients with cirrhosis often present with an elevated international normalized ratio (INR) and a prolonged PT.6 Health care providers often attempt to reverse the elevated INR by giving patients vitamin K supplementation; however, the practice of vitamin K supplementation in cirrhotic patients is not well defined, and its true value appears questionable.

This article attempts to put into perspective both the unique coagulopathic imbalances that are seen in cirrhosis and the relative utility of administering vitamin K to these patients simply because they present with elevated INRs.7 Following are five case reports we saw at our institution that exemplify the variability in response to vitamin K in these situations.

CASE REPORTS

The following five cases were identified via our gastro-enterology/hepatology service. They illustrate different scenarios that show a diversity of outcomes involving the presence or absence of vitamin K use in cirrhosis.

Patient 1

A 60-year-old female with a history of chronic kidney disease (CKD), hepatitis C, and alcoholic cirrhosis presented from an outside hospital for management of decompensated liver failure, acute renal failure, and a urinary tract infection. Her model for end-stage liver disease (MELD) score upon admission was 33, with Child-Pugh class C cirrhosis. She was admitted with an INR of 2.4. Over her six-day stay, she showed clinical improvement, and her INR gradually decreased to 1.6 without vitamin K administration.

Patient 2

A 67-year-old female with a history of hypertension, hypothyroidism, and alcoholic cirrhosis was transferred from an outside hospital for the treatment of jaundice. Her INR upon admission was 1.9, her Child-Pugh class was C, and her MELD score was 38. She received three daily doses of intravenous (IV) vitamin K 10 mg, and her INR increased to 2.1 at five days after admission.

Patient 3

A 60-year-old female with a history of CKD, type-2 diabetes mellitus, and non-alcoholic steatohepatitis cirrhosis was transferred from an outside hospital for hypoxia with a MELD score of 34 and Child-Pugh class C cirrhosis. She had an INR of 2.1 on admission. She then received three daily doses of oral vitamin K 10 mg. Although her INR initially fell to 1.7 by the last day of vitamin K, it had increased to 2.3 the following day.

Patient 4

A 36-year-old female with a history of anxiety, depression, gastroesophageal reflux disease, irritable bowel syndrome, and decompensated autoimmune hepatitis was transferred from an outside hospital for hernia management. She had a MELD score of 27 and Child-Pugh class C cirrhosis. Her initial INR was 2.0. She received one dose of oral vitamin K 10 mg and one
dose of IV vitamin K 10 mg on consecutive days. Her INR decreased to 1.7.

**Patient 5**

A 27-year-old male with a history of primary sclerosing cholangitis and ulcerative colitis presented to the emergency department with melena. He had Child-Pugh class C cirrhosis upon admission, with an INR of 3.8. After two doses of IV vitamin K 10 mg, his INR fell to 1.0.

Table 1 lists the Child-Pugh calculation parameters for each of these patients, and Table 2 summarizes the changes in INR related to the commensurate vitamin K regimens.

**METHODS**

**Study Search and Selection**

The medical literature was searched using PubMed with the following strategies: (vitamin K1 or phytomenadione) and liver and anticoagulants and (treatment or therapy), and (vitamin K1 or phytomenadi-one) and liver[mh] and anticoagulants and (treatment or therapy) for the years 1981 through 2017. The articles were limited to the English language. Each article’s reference list was reviewed for additional articles that may have been relevant to the topic. Published articles relevant to vitamin K use in patients with cirrhosis were reviewed and summarized.

**OVERVIEW OF THE COAGULATION CASCADE IN CIRRHOSIS**

**Hemostatic Changes in Cirrhosis**

As previously stated, cirrhosis is now better understood as an imbalance within the coagulation cascade. This precarious imbalance increases the risk of both bleeding and clotting in patients with cirrhosis. Table 3 summarizes the imbalances in the hemostasis equation. Overall, six proposed mechanisms may contribute to hemostatic imbalance: 1) decreased synthesis of procoagulant and anticoagulant proteins by the liver, 2) impaired clearance of activated coagulation factors, 3) platelet disorders, 4) nutritional deficiency, 5) fibrinolysis with dysfibrinogenemia, and 6) disseminated intravascular coagulation (DIC).

**Decreased Synthesis and Impaired Clearance of Clotting Factors**

One important aspect of the hemostatic abnormalities in cirrhosis includes modifications in both the procoagulant and anticoagulant protein sides of the cascade. On the anticoagulant side, there is a reduction in the synthesis of preactivated factors II, V, VII, IX, X, and XI. Conversely, on the procoagulant side, there is a decrease in antithrombin III and proteins C and S, with an increase in factor VIII and von Willebrand factor.

In cirrhosis, the underlying reduction in viable hepatocytes results in a relatively reduced production of these pre-vitamin K activated coagulation factors. As the liver is almost entirely responsible for the synthesis of all the coagulation factor precursors, patients with cirrhosis have decreased circulating concentrations of all the inactivated coagulation factors, except factor VIII. Factor VIII is also produced extrahepatically in endothelial cells. In cirrhosis, factor VIII levels are typically elevated because, like all other activated clotting proteins, factor VIII also requires hepatic clearance. With cirrhosis, the liver clears less of the activated von Willebrand factor and factor VIII, resulting in the further elevation of these proteins in relation to the other coagulation factors. Proteins C and S are also synthesized in the liver and circulate in decreased concentrations in cirrhosis.

**Platelet Disorders**

Splenomegaly is another manifestation of cirrhosis, and it occurs secondary to the “back pressures” that result in the splanchnic circulation from portal hypertension. The enlargement of the spleen, as well as other factors, leads to thrombocytopenia with platelet counts commonly below 100,000/mm³, but rarely lower than 30,000 to 40,000/mm³. Furthermore, there are lower circulating levels of thrombopoietin, which is a glycoprotein hormone produced in the liver that is responsible for the metamorphosis of megakaryocytes into mature platelets. Despite these relatively low platelet counts, spontaneous bleeding in cirrhosis is much less common than one would predict. One explanation for the disparity is that an increase in von Willebrand factor increases the adhe-
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Table 3 Imbalances of the Coagulation Cascade in Cirrhosis

<table>
<thead>
<tr>
<th>Increased Bleeding Risk</th>
<th>Increased Clotting Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Procoagulants: Factors II, V, VII, IX, X, XI</td>
<td>Decreased Anticoagulants: Antithrombin III, Protein C, Protein S</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Increased Procoagulants: Factor VIII, von Willebrand Factor</td>
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Potze et al. compared the changes seen in in vitro anticoagulation assays with unfractionated heparin and low-molecular-weight heparin when added to the plasma of patients with cirrhosis and patients without cirrhosis. At baseline, they found that the INR was significantly increased in patients with cirrhosis, and that the increase mirrored the severity of cirrhosis. Patients with Child-Pugh class C cirrhosis had the highest INRs, with a mean of 1.5. The aPTT was also prolonged in patients with cirrhosis by 3 to 7 seconds, but it did not follow the same linear disease-severity trend. A study by Fuentes et al. compared the anticoagulation assays of patients with cirrhosis who were receiving heparin to patients without cirrhosis who were receiving heparin. At baseline, the INR was found to be significantly higher in the group with cirrhosis than in the group without cirrhosis (1.6 vs. 1.2, P < 0.001).

Relative Venous Thromboembolism Risks in Patients with Cirrhosis

Dabbagh et al. performed a retrospective cohort study over seven years that included 190 patients with chronic liver disease at a tertiary university hospital. They measured the incidence of venous thromboembolism (VTE) during the patients’ stay in hospital. Patients were divided into quartiles by their highest INR upon admission. VTE incidence among the 190 patients was 6.3%, and there was no significant difference in the incidence of VTE between the INR quartiles. However, 50% of the VTE cases occurred in patients with cirrhosis who had not received anticoagulation at baseline and who had an INR above 1.6. Even patients with cirrhosis and an INR higher than 2.2 experienced VTE. The study concluded that an increase in INR due to chronic liver disease does not protect against VTE.

Søgaard et al. completed a case-control study of VTE incidence over 25 years, from 1980 to 2005, which included 67,519 patients who had unprovoked VTE and 308,604 population controls. The relative risk of VTE was 2.06 in patients who had cirrhosis and 2.10 in patients who had non-cirrhotic liver disease, thus revealing that patients with liver disease have a twofold increased incidence of VTE compared to the general population.

Wu and Nguyen performed a similar population-based study in U.S. inpatients from 1998 to 2006. After comparing VTE prevalence among patients with cirrhosis to those without cirrhosis, they determined that there was a higher risk for VTE in patients with compensated and decompensated cirrhosis up to the age of 45 years. The odds ratios (ORs) for VTE incidence in compensated cirrhosis and decompensated cirrhosis were 1.23 and 1.39, respectively. Patients older than 45 years with compensated cirrhosis had a lower risk of developing VTE (OR, 0.90) compared to the general population. Meanwhile, those older than 45 years with decompensated cirrhosis experienced an equal risk of VTE (OR, 0.97) compared to the general population. The overall prevalence of VTE was 0.78% among patients without cirrhosis, 0.81% among patients with compensated cirrhosis, and 0.82% among patients with decompensated cirrhosis. Of note, VTE was associated with a higher mortality among patients with compensated cirrhosis (OR, 2.16; 95% CI, 1.96–2.38) and among patients with decompensated cirrhosis (OR, 1.66; 95% CI, 1.47–1.87).

Nutritional Deficiency

Nutritional deficiency is common in patients with cirrhosis, especially those with coexisting biliary disease. The ensuing reduction in bile production and flow leads to decreased intraluminal concentrations of biliary salts. This results in the decreased absorption of fat-soluble vitamins, including vitamin K. Vitamin K is responsible for the production of factors II, VII, IX, and X because of its role as a cofactor in the gamma-carboxylation of glutamic acid residues. We discuss vitamin K deficiency in greater detail later in this article.

Fibrinolysis, Dysfibrinogenemia, and Disseminated Intravascular Coagulopathy

The presence of fibrinolysis and dysfibrinogenemia, which correlate to the severity of chronic liver disease, are other mechanisms leading to hemostatic imbalance. Fibrinolysis results from the decreased hepatic clearance of tissue plasminogen activator, which subsequently leads to an increased thrombus breakdown. About 31% of patients with compensated cirrhosis experience fibrinolysis, compared to 93% of patients with ascites. Patients present with normal fibrinogen, and cirrhosis without DIC, and cirrhosis. In DIC, factor VIII levels are decreased along with all other coagulation factors, but in cirrhosis without DIC, factor VIII levels remain elevated.

Coagulation Tests in Cirrhosis

As previously mentioned, many routinely collected coagulation tests are increased at baseline in patients with cirrhosis. Studies have shown an increase in PT, INR, and activated partial thromboplastin time (aPTT) in patients with cirrhosis. A study by Søgaard et al. compared the anticoagulation assays of patients with cirrhosis who were receiving heparin to patients without cirrhosis who were receiving heparin. At baseline, the INR was found to be significantly higher in the group with cirrhosis than in the group without cirrhosis (1.6 vs. 1.2, P < 0.001).
Finally, a case-control study of patients in a tertiary care hospital was completed by Gulley et al. The study included 963 patients with cirrhosis and 12,405 controls. The incidence of VTE in patients with cirrhosis was 1.8% compared to 0.9% in the control patients (P = 0.007). A multivariate analysis was completed that did not show an increased risk of VTE with cirrhosis but indicated that PTT (OR, 0.88; P = 0.04) and serum albumin (OR, 0.47; P = 0.03) are independently predictive of VTE in cirrhosis.11

OVERVIEW OF VITAMIN K

Vitamin K “Pharma-K-netics”

Vitamin K is a fat-soluble vitamin that acts as a cofactor in the gamma-carboxylation of multiple glutamate residues. The gamma-carboxylated glutamate residues allow the formation of coagulation factors and post-translational calcium binding to gamma-carboxylated proteins such as prothrombin, factors VII, IX, and X, protein C, and protein S, as well as those proteins found in bone and vascular smooth muscle.12 Vitamin K has two forms: phytonadione or phylloquinone (vitamin K1) and menaquinone (vitamin K2). Vitamin K1 is found in our diet from both animal and vegetable sources, including green leafy vegetables, fruits, oils, and nuts, with the average daily intake being 100 mcg/dL. Vitamin K2 is synthesized by bacterial flora and is found in our hepatic tissue.12 Vitamin K1 can be converted to vitamin K2, which then accumulates in extrahepatic tissues.13

Vitamin K stores are maintained both through daily dietary intake and enterohepatic recirculation of menaquinones produced by the endogenous bacterial flora. Vitamin K deficiency is most often the result of decreased absorption through small intestinal disease, surgical resection, or biliary obstruction. Antibiotics and diarrheal illness may decrease the counts of endogenous menaquinone-producing gastrointestinal bacterial flora.14 Finally, drugs that block vitamin K activation, such as warfarin, can also decrease vitamin K stores.12

Vitamin K can be administered orally, intravenously, intramuscularly, or intramuscularly for patients with a deficiency or if the patient is actively bleeding. Common doses range from 1 mg to 10 mg orally and from 0.5 mg to 10 mg intravenously. Intramuscular and subcutaneous routes tend to be avoided due to the risk of hematoma and variable absorption, respectively. Vitamin K is absorbed in the small intestine in the presence of bile and is metabolized by the liver before being excreted in either urine or feces. The onset of action of oral vitamin K is six to 10 hours, with a peak effect around 24 to 48 hours. IV vitamin K has an onset of action of one to two hours, with a peak effect occurring between 12 and 24 hours. The elimination half-life of vitamin K varies from 26 to 190 hours.15,16

Measurement of Vitamin K Levels

There are three approaches to measuring vitamin K, including PT, vitamin K1 levels, and the proteins induced by vitamin K absence or antagonist-II (PIVKA-II) levels. First, PT measures the amount of time it takes for blood to coagulate and that is prolonged in the absence of vitamin K. It measures changes in coagulation factors I, II, V, VII, and X, of which II, VII, and X are affected by the presence of vitamin K for gamma-carboxylation. PT tends to underestimate the deficiency of vitamin K because of its inability to detect a change until the coagulation factors are decreased by 30% to 40%.17

The second approach is through the measurement of vitamin K1 levels. These levels measure vitamin K in the blood, but not total body vitamin K stores. This idiosyncrasy in the test results in the decreased sensitivity and variable efficacy in determining a true vitamin K deficiency.

The third method of measuring vitamin K is through an enzyme-linked immunosorbent assay kit that measures the under-carboxylated precursors of the vitamin K cycle, known as proteins induced by PIVKA-II. Levels of PIVKA-II are the most sensitive marker of vitamin K status, since they are elevated only in the absence of vitamin K. When there is a deficiency in vitamin K, decreased gamma-carboxylation of vitamin K coagulation factors occurs, resulting in the elevation of the precursor proteins. Normal PIVKA-II levels are considered to be below 3 ng/mL, and vitamin K deficiency is diagnosed with levels that are greater than 3 ng/mL.19 One study, which used specific human prothrombin immunoassays, determined that more than 90% of patients with liver disease had detectable undercarboxylated proteins in their plasma. This was independent of any bleeding disorder.19

Vitamin K Deficiency in Cholestatic Liver Disease and Cirrhosis

Vitamin K deficiency is common in certain types of liver disease. Deficiency can be caused by decreased absorption in the small intestine from decreased bile flow or small intestine disease, decreased oral intake caused by poor nutritional status or chronic illness, the decreased ability of the liver to complete the vitamin K cycle as a result of decreased function, or the increased use of antibiotics, which results in the decreased production of menaquinones by gastrointestinal flora.20

Two studies aimed to determine the presence of vitamin K deficiency in liver disease.27,28 Strople et al. investigated the prevalence of subclinical vitamin K deficiency in pediatric and adult patients with cholestatic liver disease.27 This cross-sectional study measured PIVKA-II levels in 31 patients with cholestasis, which was defined as a direct bilirubin level greater than 1 mg/dL and/or serum bile acids greater than 30 μmol/L. Patients were excluded if they had compensated cirrhosis or severe coagulopathy, defined as an INR greater than 2, since they were deemed unlikely to be responsive to vitamin K supplementation. All of the patients with increased INRs had increased plasma PIVKA-II levels. These levels positively correlated with serum conjugate bilirubin (P < 0.001), bile acids (P = 0.002), aspartate transaminase/alanine transaminase (P = 0.01/0.02), PT (P = 0.02), and INR (P = 0.02). Levels of 25-hydroxy-vitamin D were negatively correlated with PIVKA-II levels likely because bile acids are required for the absorption of fat-soluble vitamin D. Of note, over 70% of the patients with elevated plasma PIVKA-II levels had received oral vitamin K supplementation. This study found that vitamin K deficiency persisted with oral vitamin K supplementation, providing further evidence that bile is required for the absorption of vitamin K and that oral supplementation does not correct the deficiency. The study also provided evidence to support the notion that plasma PIVKA-II levels correlate with INR and liver function tests.18
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Mager et al. sought to determine the prevalence of subclinical vitamin K deficiency in children with mild to moderate chronic liver disease. They included 43 children with mild to moderate chronic cholestatic liver disease and 29 children with mild-to-moderate noncholestatic liver disease. They compared the study groups to 44 healthy children. Plasma PIVKA-II levels were used to determine vitamin K status in these patients, with deficiency defined as a level above 3.0 ng/dL. The mean plasma PIVKA-II levels were 61.9 ng/dL in cholestatic disease, 1.2 ng/dL in noncholestatic disease, and 2.1 ng/dL in healthy children (P < 0.002). All control subjects had plasma PIVKA-II levels below 3 ng/dL. Although 21 children with cholestatic liver disease had elevated plasma PIVKA-II levels, only two of them had a prolonged PT, showing that the measurement of PT underestimated vitamin K deficiency in these patients. Overall, vitamin K deficiency directly correlated with an increasing severity of cholestasis, and with a minimal vitamin K deficiency in patients without cholestatic liver disease.

These studies validated the correlation between plasma PIVKA-II levels, INR, and liver function tests. They also support the notion that patients with cirrhosis are less likely to have vitamin K deficiency than those with the most common forms of cholestatic liver disease.

VITAMIN K IN CIRRHOSIS

The administration of vitamin K to attempt to reverse an elevated INR in a patient with cirrhosis has been a routine practice throughout the U.S. for over four decades. The rationale for this decision, even in the face of minimal evidence of any benefit, is likely based upon two simple but somewhat flawed tenets. First, despite evidence to the contrary, it is often thought that patients with cirrhosis are categorically vitamin K-deficient. Second, there exists a perception that the administration of vitamin K is harmless.

It is challenging to determine the origin of this practice in the medical literature. One review article focuses on the use of procoagulant therapeutics in liver disease, recommending the use of vitamin K repletion due to the prevalence of vitamin K deficiency in liver disease. However, they also comment on the notion that this repletion is not supported by clinical outcomes, and most research shows that replacement is not an effective treatment for the coagulopathy of liver disease, especially in cirrhosis.

Studies on the Use of Vitamin K

As stated earlier, the rationale and research behind the use of vitamin K to correct coagulopathy in cirrhosis is limited. We will review three studies that investigated the effect of vitamin K administration in patients with cirrhosis.

Saja et al. aimed to assess the effect of vitamin K administration on various coagulation parameters. This prospective multicenter study separated 89 patients into five groups, including patients with cirrhosis, hepatitis B virus, chronic hepatitis B or C virus, hepatocellular carcinoma (HCC), and healthy controls. Parameters assessed included the levels of vitamin K-dependent factor VII, protein C, protein S, and PIVKA-II, both at baseline and 72 hours after receiving 10 mg of subcutaneous vitamin K1. Other parameters assessed included PT, aPTT, TT, fibrinogen, and free protein S. At baseline, all groups had decreased fibrinogen, factor VII, protein C, and protein S (P < 0.0001). The PT was prolonged in the cirrhosis and HCC groups when compared to controls (P < 0.0001). Compared to the baseline measurements, vitamin K significantly decreased the PT and aPTT in the cirrhosis group but did not affect any of the other measured parameters. PT and aPTT decreased by 13.5 seconds and 13.6 seconds, respectively. Interestingly, those decreases were not mirrored by other vitamin K-dependent proteins such as protein C, protein S, and factor VII. In fact, in contrast to the expected increase, protein C actually decreased after vitamin K administration.

Regarding the PIVKA-II levels in this study, patients with hepatocellular carcinoma were the only group with increased levels at baseline. This is likely a result of the production of PIVKA-II proteins by the tumor cells. Failure to show an increase in PIVKA-II levels at baseline in cirrhosis suggests that vitamin K deficiency does not play an integral role in the coagulopathy of these patients. Of note, the PIVKA-II levels did show a statistically significant reduction in the patients with cirrhosis (P < 0.024) after vitamin K administration. However, this is unlikely to be clinically significant as the PIVKA-II levels between the control group and the patients with cirrhosis were not statistically different at baseline (P > 0.05).

Blanchard et al. reviewed blood samples from 15 healthy patients, 23 patients receiving warfarin, 4 patients with vitamin K deficiency, and 28 patients with liver disease. They determined the PT, elevated levels of undercarboxylated prothrombin, and abnormal prothrombin. Fourteen patients had cirrhosis, and seven of them received vitamin K; the administration of vitamin K did not correct the PT, nor did it decrease the levels of undercarboxylated prothrombin. Because of the stable PT after vitamin K administration, it is possible that the mechanism resulting in decreased vitamin K-dependent, precursor proteins is not entirely owing to vitamin K deficiency.

Finally, a study by Feldshon et al. determined that impaired synthesis of coagulation proteins was the primary reason for the coagulopathy of chronic liver disease. The authors concluded that impaired carboxylation was not an integral component of the coagulopathy of liver disease, and that vitamin K administration did not improve any of the coagulation parameters.

CONCLUSION

Hepatic cirrhosis leads to a complicated pathophysicsology that results in a plethora of detrimental clinical manifestations. One of the most notable of these is coagulopathy. This coagulopathy is best described as a delicate imbalance between the procoagulant and anticoagulant factor cascades. Despite there being no compelling evidence of true benefit, vitamin K is frequently administered in an attempt to correct the elevated PT/INR levels that are often seen in cirrhotic patients.

Based upon our review of the available literature, it appears unlikely that deficiency of vitamin K is significantly responsible for the coagulopathy of cirrhosis; and even if it were a factor, because of the underlying impairment in synthesis of the coagulation precursor proteins, the administration of vitamin K has not been found to consistently lower the INR. The studies cited here, along with the five cases presented earlier in this article, support the notion that vitamin K does not seem to add clinical benefit in the setting of cirrhotic coagulopathy.
It is also unclear whether the administration of vitamin K is safe in these patients, as it could theoretically tip the balance toward thrombosis. Further studies are needed to assess the safety and efficacy by measuring important clinical outcomes, including the incidence of clinically significant bleeding or clotting. That said, with the limited evidence to date, it is our opinion that the routine use of vitamin K to correct PT/INR in liver cirrhosis cases without significant and active bleeding should be avoided.

REFERENCES


