World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v7.i29.2906

World J Hepatol 2015 December 18; 7(29): 2906-2912
ISSN 1948-5182 (online)

MINIREVIEWS

Therapeutic and clinical aspects of portal vein thrombosis in patients with cirrhosis

Massimo Primignani, Giulia Tosetti, Vincenzo La Mura

Massimo Primignani, Giulia Tosetti, U.O. Gastroenterologia ed Epatologia, IRCCS-Ca' Granda, Ospedale Maggiore Policlinico, 20122 Milano, Italy

Vincenzo La Mura, U.O. Medicina Interna, IRCCS-San Donato, Dipartimento di Scienze Biomediche per la Salute, Università degli studi di Milano, 20097 Milan, Italy

Author contributions: Primignani M contributed to review concept and design; all authors contributed to drafting of the manuscript.

Conflict-of-interest statement: No potential conflict of interest.

Correspondence to: Massimo Primignani, MD, PhD, U.O. Gastroenterologia ed Epatologia, IRCCS-Ca' Granda, Ospedale Maggiore Policlinico, via F. Sforza 35, 20122 Milano, Italy. massimo.primignani@policlinico.mi.it
Telephone: +39-02-55035432
Fax: +39-02-50320410

Received: July 3, 2015
Peer-review started: July 9, 2015
First decision: August 25, 2015
Revised: November 8, 2015
Accepted: December 1, 2015
Article in press: December 2, 2015
Published online: December 18, 2015

Abstract

Portal vein thrombosis (PVT) is a frequent complication in cirrhosis, particularly in advanced stages of the disease. As for general venous thromboembolism, risk factors for PVT are slow blood flow, vessel wall damage and hypercoagulability, all features of advanced cirrhosis. Actually, the old dogma of a hemorrhagic tendency in cirrhosis has been challenged by new laboratory tools and the clinical evidence that venous thrombosis also occurs in cirrhosis. The impaired hepatic synthesis of both pro- and anticoagulants leads to a rebalanced hemostasis, more liable to be tipped towards thrombosis or even bleeding. Conventional anticoagulant drugs (low molecular weight heparin or vitamin K antagonists) may be used in cirrhosis patients with PVT, particularly in those eligible for liver transplantation, to prevent thrombosis progression thus permitting/facilitating liver transplant. However, several doubts exist on the level of anticoagulation achieved as estimated by coagulation tests, on the efficacy of treatment monitoring and on the correct timing for discontinuation in non-transplant candidates, while in transplant candidates there is expert consensus on continuing anticoagulation until transplantation. The recent introduction of direct acting oral anticoagulant drugs (DOACs) in other clinical settings generates much interest on their possible application in patients with cirrhosis and PVT. However, DOACs were not evaluated yet in patients with liver disease and cannot be recommended for the present time.

Key words: Portal vein thrombosis; Coagulopathy; Hypercoagulopathy; Direct acting oral anticoagulant drugs; Cirrhosis

Core tip: Impaired liver synthesis of both pro- and anticoagulants maintains a haemostatic balance in advanced liver disease, but this balance is more unstable than in healthy subjects and can be easily tipped towards thrombosis or bleeding. Portal vein thrombosis

(PVT) frequently occurs in advanced stages of cirrhosis and, if occlusive or extensive, may complicate or impede liver transplant. Therefore, prevention and treatment of PVT are frequent issues in cirrhosis patients, particularly in those eligible to liver transplant. Current treatments are with low molecular weight heparin or vitamin K antagonists and should be continued until transplantation in liver candidates, whereas no consensus exists regarding the duration of anticoagulation in non-transplant candidates.

Primignani M, Tosetti G, La Mura V. Therapeutic and clinical aspects of portal vein thrombosis in patients with cirrhosis. *World J Hepatol* 2015; 7(29): 2906-2912 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i29/2906.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i29.2906

INTRODUCTION

Portal vein thrombosis (PVT) is a rare event in the general population, but is frequent in patients with cirrhosis, particularly in the advanced stages of the disease. Actually, the prevalence of PVT parallels the progression of cirrhosis, being less than 1% in patients with compensated disease, but 8%-25% in liver transplant candidates[1-4] and further increases when the disease is complicated by the occurrence of hepatocellular carcinoma. In this review article we describe the risk factors for PVT in cirrhosis, discuss the controversial clinical impact of PVT on the natural history of cirrhosis and the current indications for PVT prevention or treatment.

RISK FACTORS AND PATHOGENESIS OF PVT IN CIRRHOSIS

Slow blood flow, vessel wall damage and hypercoagulability, the classical triad of mechanistic factors for general venous thromboembolism identified by Virchow more than 150 years ago, are the perceived risk factors also for PVT in cirrhosis. Indeed, slowing of portal blood velocity, which occurs with the progression of liver disease, has been identified as a risk factor for PVT[5].

As for venous thromboembolism hypercoagulability has been reported at increased rate in some studies, but not in others. Causes include factor V Leiden and prothrombin gene mutation, hyperhomocysteinemia, protein C and protein S deficiencies, and elevated factor Ⅷ[6,7].

More in general, the long standing belief of a "spontaneous anticoagulation" in cirrhosis, due to the reduced hepatic synthesis of coagulant factors, and recognized by the prolongation of the classical coagulation tests prothrombin time (PT) and activated partial thromboplastin time (APTT), has recently been revised in favour of a new concept of "rebalanced haemostasis" in cirrhosis. Indeed, PT and APTT, due to their design, are much more sensitive to the procoagulants, than to the naturally occurring anticoagulants protein C, protein S, and antithrombin, which are also synthesized by the liver and are decreased, often severely, in plasma from cirrhosis patients. Protein C, *in vivo*, is activated by thrombin and quenches thrombin generation in order to limit the activation of the coagulation cascade. However, for Protein C being activated, the presence of thrombomodulin, its endothelial receptor, is required. Since thrombomodulin is not present in the PT and APTT reagents, it appears that such test are unsuitable to assess the balance of pro- and anticoagulants in plasma from cirrhosis patients and to predict bleeding events[8-10]. Recently, global coagulation tests able to account for both pro- and anticoagulants, such as the thrombin generation test, indicate that plasma from patients with cirrhosis generates equal amounts of thrombin as compared to plasma from healthy subjects, if measured in the presence of thrombomodulin[11]. However, since also platelets, besides their role in primary haemostasis, support thrombin generation by assembling activated coagulation factors on their surface, a normal thrombin generation is still found if a sufficient platelet count of around 60 × 10^9/L is preserved[12].

Further evolution of research suggests, particularly in advanced cirrhosis, the occurrence of a procoagulant imbalance whose biomarker is the resistance to the inhibition of thrombin generation, expressed by the increased ratio of thrombin generation with/without thrombomodulin. The increased ratio between Factor Ⅷ (a strong procoagulant driver, markedly increased in cirrhosis plasma) and Protein C (a strong inhibitor of thrombin generation and of activated factor Ⅷ, severely decreased in cirrhosis plasma) appears to be the biological background of such imbalance[13].

In summary, PT or APTT can no longer be regarded as indexes of hypocoagulability in patients with cirrhosis. By converse, cirrhosis can be viewed as an acquired prothrombotic condition, a new concept that better fits with the tendency to PVT, or the increased rate of venous thromboembolism occurring in cirrhotic patients when exposed to risk factors[14].

CLINICAL IMPACT OF PVT IN CIRRHOSIS

The impact of PVT on the natural history of cirrhosis is controversial, as several studies evaluating the clinical outcome of cirrhosis patients after the diagnosis of PVT gave discordant results[4,15-18]. In fact, some studies suggest that PVT may progress to complete occlusion and/or extend to other splanchnic vessels in 40%-70% of cases. In addition, patients with PVT appear to have more than threefold increased risk of failure to control variceal bleeding[17] and a reduced post-transplant survival[4] suggesting that the presence of PVT in advanced liver disease is associated with critical outcomes. On the opposite hand, a recent multicenter study, showed, in a large series of patients, that the

incidence of PVT, most often non-occlusive, did not influence the clinical outcome and was associated with a high rate of spontaneous recanalization[19].

PROPHYLACTIC TREATMENT

The recent finding that prophylactic doses of enoxaparin, besides preventing PVT without increasing the rate of bleeding, also reduced bacterial translocation and the incidence of further decompensation in patients listed for liver transplantation[20] suggests a role for anticoagulants in cirrhosis wider than previously expected. Since activated coagulation factors have other targets, besides clotting, and promote fibrogenesis by acting on platelets, endothelial cells and stellate cells, the role of anticoagulants might extend beyond the prevention or treatment of PVT in cirrhosis, towards the prevention of progression of cirrhosis itself[21].

Larger, confirmatory studies are needed before a widespread use of enoxaparin in patients with cirrhosis permeates clinical practice. However, the growing evidence from clinical studies and the finding of normal/increased amounts of thrombin generated *in vitro* demonstrates that the so-called "auto anticoagulation" of patients with cirrhosis is a false dogma.

This new concept generates consequences in clinical practice. For instance, thromboprophylaxis for the prevention of deep vein thrombosis should be given to cirrhosis patients, as to the general population, when exposed to such risk factors as immobilization, cancer or surgery[22,23]. However, such strategy is still not generally adopted in cirrhosis, due to the perceived risk of hemorrhage.

As far as PVT is concerned, anticoagulation might be indicated for treating or preventing PVT in particular settings, such as the patients eligible or listed for liver transplant or those undergoing hepatic resection[3,24].

However, although clinical data and modern global coagulation tests indicate that patients with cirrhosis have a rebalanced hemostasis or even a prothrombotic phenotype, particularly in advanced stages of the disease, this balance may be weak and can be tipped towards thrombosis or haemorrhage by ensuing comorbidities, as bacterial infections or renal failure. In addition, patients with cirrhosis may have severe thrombocytopenia, which adds risk to anticoagulation therapy.

Therefore, several warnings must be considered before implementing a more liberal use of anticoagulants in patients with liver cirrhosis and the risks and benefit of anticoagulation in these patients must be carefully weighted. These warnings regard safety, monitoring and, to some extent, the proper indication of anticoagulation in cirrhosis patients with PVT.

STRATEGIES OF TREATMENT IN PATIENTS WITH OVERT PVT

Concerning efficacy and safety of anticoagulation in cirrhosis patients with established PVT, the available data refer to five case series including, overall, 163 subjects, mostly with partial PVT[4,24-27] (Table 1). At month-6 of therapy, complete or partial recanalization occurred in 33%-45%, while thrombus progression developed in less than 10%. Factors predicting recanalization were recent onset (< 6 mo) of the thrombus and partial PVT. Treatment prolongation after six months was associated with a higher rate of recanalization and a lower incidence of thrombosis progression or recurrence. Most patients had past bleeding or high-risk varices, and received endoscopic therapy with or without beta-blockers prior to anticoagulation. Bleeding occurred in 5% of the patients. After stopping anticoagulation, the benefit declined rapidly, as PVT recurred in up to 40% of patients. Overall, these data indicate a favorable risk/benefit ratio.

However, although these good safety data for portal hypertension-related bleeding in patients treated with anticoagulants, the number of patients enrolled in clinical studies is still low to allow firm conclusions on the safety of prolonged anticoagulation treatment, and few data on non-portal hypertension-related bleedings are available. In addition, more data on the safety of anticoagulation in patients with advanced stages of cirrhosis are required.

The use of vitamin K anatagonists and low molecular weight heparins

As far as the anticoagulant to choose for patients with cirrhosis is concerned, vitamin K antagonists (VKA) and low molecular weight heparin (LMWH) are those currently used, although several doubts exist on the required doses, on the level of anticoagulation achieved as estimated by coagulation tests, and on the efficacy of treatment monitoring. In fact, LMWH monitoring may be complicated by the low levels of antithrombin frequently occurring in these patients[25] and by analytical troubles affecting the anti-factor Xa measurement in patients with liver disease[28,29]. As for VKA in cirrhosis patients, one may consider that the PT-INR was originally intended for patients on VKA to harmonize the PT results from different laboratories and thromboplastins, but is less valid for patients with cirrhosis as their coagulopathy is different from that caused by VKA[30-33]. In addition, the frequently encountered baseline PT prolongation in cirrhotic patients casts doubts on whether the level of anticoagulation achieved is correctly represented by the PT.

This notwithstanding, VKA and LMWH appear to be equally effective and relatively safe in patients with cirrhosis, although long-term regimens have not been evaluated yet. LMWH, although less practical because of the need for subcutaneous injections, can be used until transplantation. Importantly, and at difference with VKA, it does not interfere with the MELD score.

Conversely, VKA can be given orally, but interfere with the MELD score. Anticoagulation can be reversed rapidly at the time of transplantation by the administration of

Table 1 Studies on management of portal vein thrombosis in cirrhotic patients

Ref.	Study type	PVT	Number anticoagulate patients	Number controls	Typeanticoagulant	Duration anticoagulation	Repermeation/stabilization/ progression of thrombosis in anticoagulate patients	Repermeation/stabilization/ progression of thrombosis in control patients	Bleeding complications in anticoagulate patients	Bleeding complications in controls
Francoz *et al*[4]	Proscpective; Case control	29	19	10	VKA (target INR 2-3)	Mean 8.1 mo	8/10/1	0/4/6	1 variceal bleeding after EBL	NA
Amitrano *et al*[25]	Prospective	28	28	-	Enoxaparin 200 UI/kg per day	6 mo in repermeation, until end follow up in partial responders	21/5/2	-	1 anemia in PHG	-
Senzolo *et al*[24]	Prospective; Case control	56	35	21	Nadroparin 95 antiXa U/kg twice a day	6 mo after complete repermeation, until the end of follow up in other patients	21/7/5	1/5/15	1 variceal bleeding; 1 cerebral haemorrage; 1 haematuria; 1 epistaxis	5 variceal bleeding
Delgado *et al*[26]	Retrospective	55	55	-	VKA (8 patients); VKA → LMWH (21 patients); LMWH (26 patients)	Median 6.8 mo (range 1-56 mo)	33/22/0	-	6 variceal bleeding; 1 obscure gastrointestinal bleeding; 1 lower gastrointestinal bleeding; 1 oral bleeding after dental extraction	-

PVT: Portal vein thrombosis; VKA: Vitamin K antoagonists; LMWH: Low molecular weight heparin; NA: Not available; PHG: Portal hypertensive gastropathy; EBL: Endoscopic bend ligation; INR: Internatiol normalized ratio.

fresh frozen plasma. A platelet count < 50 × 10^9/L and the use of VKA were the only factors more frequently observed in patients with a bleeding episode suspected to be related to anticoagulation therapy[26].

Direct oral anticoagulant agents: Where we are

Many of the warnings related to LMWH and VKA could be overcome by the recently introduced direct acting oral anticoagulant drugs (DOACs), which inhibit thrombin (Dabigatran) or activated factor X (Rivaroxaban, Apixaban and Edoxaban). These drugs have the advantages of oral administration, fixed dose and no need of laboratory monitoring[34]. Moreover, their mechanism of action is independent of antithrombin, which is necessary for LMWH be effective, but may be severely impaired in cirrhosis patients. Finally, DOACs do not interfere with the MELD score. However for now, anticoagulation induced by DOACs is not quickly reversible and this may be a concern in case of bleeding. Another potential issue is renal function; DOACs, especially dabigatran, have predominantly renal excretion and impairment of renal function, frequently observed in patients with cirrhosis, could cause drug accumulation[35].

Notwithstanding, DOACs, which are currently used to prevent venous thromboembolism in orthopedic surgery and, at therapeutic dosages, in atrial fibrillation and deep vein thrombosis[36-38], appear to be as effective as LMWH or warfarin, with less bleeding complications. However, although the overall lower bleeding rate in patients treated with DOACs *vs* VKA, the incidence of gastrointestinal bleeding appears to be slightly but definitively increased, with an absolute risk of 2.6% *vs* 2%[39]. This might be a matter of concern in cirrhosis patients for the future. For now, whether DOACs are safe and effective in cirrhosis is unknown, as patients with abnormal liver function tests were excluded from the studies on DOACs.

Indication to anticoagulation: Critical issues

A further point refers to the proper indication of anticoagulation in patients with PVT and cirrhosis. Several issues need consideration: The grade (partial or occlusive) and

extent of PVT, its clinical presentation and the assumed consequence on the outcome of cirrhosis, and, notably, whether the patient is eligible or not for liver transplant.

Firstly, PVT occurring in cirrhosis patients is often partial and asymptomatic, accidentally detected at ultrasound evaluation during follow-up. For this PVT type there is no evidence from prospective studies[19,40,41] of a causal relationship between its occurrence and worsening of the disease. In addition, the outcome of partial PVT, when assessed prospectively, appears to be highly variable, with either spontaneous progression or regression[41]. In other instances, abdominal pain, gastrointestinal bleeding, development or worsening of ascites or hepatic encephalopathy are associated with the onset of PVT. In addition, intestinal infarction may occur. Such clinical presentation, most often related to occlusive PVT, mainly when extended proximally and deeply into the superior mesenteric vein, obviously affects the disease outcome and requires prompt anticoagulation.

A third issue regards the eligibility of the patient to liver transplant. Because of improved surgical techniques and perioperative management, liver transplant is no longer a contraindication, even in cases of extensive PVT. However, PVT causes technical difficulties in the setting of transplantation, with a negative impact on the outcome and, in some instances, may represent a definitive contraindication for transplantation.

Furthermore, the real impact of PVT on the access to the waiting list for liver transplantation is presently unknown. Therefore, the current or future eligibility of the patient to liver transplant must be considered when deciding to prescribe anticoagulants or not.

All these issues were discussed at the recent Baveno VI workshop in a session devoted to vascular diseases of the liver, where the risks and benefits of anticoagulation were thoroughly balanced. It was agreed to consider anticoagulation in potential transplant candidates with thrombosis of the main portal vein trunk or progressive PVT, in order to permit or facilitate liver transplantation and reduce post-transplant mortality and morbidity. In addition, in untreated potential transplant candidates with PVT, it was agreed to recommend an imaging follow-up every three months and anticoagulation in case of progression. As for the duration of anticoagulation, there was consensus on maintaining anticoagulation until transplantation to prevent re-thrombosis.

Conversely, for non-candidates to LT, no recommendation regarding anticoagulation treatment could be made, but it was stated that anticoagulation could be considered in selected cases, such as patients with thrombosis extended to the superior mesenteric vein or with known "strong" prothrombotic conditions[42].

Transjugular intrahepatic porto-systemic shunt: An alternative to anticoagulation?

Similarly to what is described for acute extrahepatic portal vein obstruction in non-cirrhotic patients[43], theoretically, an endovascular approach could be useful to manage PVT also in the context of cirrhosis. However, the experience in the setting of patients with cirrhosis is very limited and hampered by the additional inconvenience that the detection of PVT in this clinical setting is generally incidental and it is difficult to establish the age of the thrombus. The best described endovascular approach is the transjugular intrahepatic porto-systemic shunt (TIPS). It might represent an alternative to anticoagulation. Indeed, TIPS may be feasible in patients with PVT, particularly if the intra-hepatic branches of portal vein are patent[44,45]. Luca *et al*[45] reported a case series of 70 patients with non-tumoral PVT treated with TIPS for the management of complications due to portal hypertension. More than half of patients achieved complete recanalization and 30% a marked decrease in thrombosis, whereas no improvement occurred in only 13%. This success rate was similar to that observed for anticoagulation. Therefore TIPS may be an option in patients with contraindication to anticoagulation treatment.

CONCLUSION

Despite a long-standing faith, liver cirrhosis is not associated with hypocoagulability. Instead, hypercoagulability, particularly in advanced disease, prevails. This is confirmed by the fact that both deep venous thrombosis and, particularly, PVT occur in cirrhosis. Although PVT in cirrhosis is frequently asymptomatic and may have a variable spontaneous evolution, it may require anticoagulation treatment in patients eligible for liver transplant or in case of thrombus progression. Either LMWH or VKA can be used, appear equally effective and share a relatively good safety profile, but larger studies, involving patients with advanced disease are needed to confirm these findings. DOACs, although promising because of their mechanism of action, have not been evaluated in patients with liver disease and cannot currently be recommended.

Anticoagulants, besides their effect on clotting, appear to decrease fibrogenesis. Such finding, if confirmed in future studies, will expand the role of anticoagulants in the clinical management of cirrhosis.

REFERENCES

1 **Tripodi A**, Anstee QM, Sogaard KK, Primignani M, Valla DC. Hypercoagulability in cirrhosis: causes and consequences. *J Thromb Haemost* 2011; **9**: 1713-1723 [PMID: 21729237]

2 **Okuda K**, Ohnishi K, Kimura K, Matsutani S, Sumida M, Goto N, Musha H, Takashi M, Suzuki N, Shinagawa T. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. *Gastroenterology* 1985; **89**: 279-286 [PMID: 4007419]

3 **Yamashita Y**, Bekki Y, Imai D, Ikegami T, Yoshizumi T, Ikeda T, Kawanaka H, Nishie A, Shirabe K, Maehara Y. Efficacy of postoperative anticoagulation therapy with enoxaparin for portal vein thrombosis after hepatic resection in patients with liver cancer. *Thromb Res* 2014; **134**: 826-831 [PMID: 25156238 DOI: 10.1016/j.thromres.2014.07.038]

4 **Francoz C**, Belghiti J, Vilgrain V, Sommacale D, Paradis V, Condat B, Denninger MH, Sauvanet A, Valla D, Durand F. Splanchnic vein thrombosis in candidates for liver transplantation:

usefulness of screening and anticoagulation. *Gut* 2005; **54**: 691-697 [PMID: 15831918]
5 **Zocco MA**, Di Stasio E, De Cristofaro R, Novi M, Ainora ME, Ponziani F, Riccardi L, Lancellotti S, Santoliquido A, Flore R, Pompili M, Rapaccini GL, Tondi P, Gasbarrini GB, Landolfi R, Gasbarrini A. Thrombotic risk factors in patients with liver cirrhosis: correlation with MELD scoring system and portal vein thrombosis development. *J Hepatol* 2009; **51**: 682-689 [PMID: 19464747]
6 **Amitrano L**, Guardascione MA, Brancaccio V, Margaglione M, Manguso F, Iannaccone L, Grandone E, Balzano A. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. *J Hepatol* 2004; **40**: 736-741 [PMID: 15094219]
7 **Amitrano L**, Brancaccio V, Guardascione MA, Margaglione M, Iannaccone L, D'Andrea G, Marmo R, Ames PR, Balzano A. Inherited coagulation disorders in cirrhotic patients with portal vein thrombosis. *Hepatology* 2000; **31**: 345-348 [PMID: 10655256]
8 **Ewe K**. Bleeding after liver biopsy does not correlate with indices of peripheral coagulation. *Dig Dis Sci* 1981; **26**: 388-393 [PMID: 7249879]
9 **Boks AL**, Brommer EJ, Schalm SW, Van Vliet HH. Hemostasis and fibrinolysis in severe liver failure and their relation to hemorrhage. *Hepatology* 1986; **6**: 79-86 [PMID: 3943792]
10 **Ng VL**. Liver disease, coagulation testing, and hemostasis. *Clin Lab Med* 2009; **29**: 265-282 [PMID: 19665678 DOI: 10.1016/j.cll.2009.05.001]
11 **Tripodi A**, Salerno F, Chantarangkul V, Clerici M, Cazzaniga M, Primignani M, Mannuccio Mannucci P. Evidence of normal thrombin generation in cirrhosis despite abnormal conventional coagulation tests. *Hepatology* 2005; **41**: 553-558 [PMID: 15726661]
12 **Tripodi A**, Primignani M, Chantarangkul V, Clerici M, Dell'Era A, Fabris F, Salerno F, Mannucci PM. Thrombin generation in patients with cirrhosis: the role of platelets. *Hepatology* 2006; **44**: 440-445 [PMID: 16871542]
13 **Tripodi A**, Primignani M, Chantarangkul V, Dell'Era A, Clerici M, de Franchis R, Colombo M, Mannucci PM. An imbalance of pro- vs anti-coagulation factors in plasma from patients with cirrhosis. *Gastroenterology* 2009; **137**: 2105-2111 [PMID: 19706293]
14 **Søgaard KK**, Horváth-Puhó E, Grønbaek H, Jepsen P, Vilstrup H, Sørensen HT. Risk of venous thromboembolism in patients with liver disease: a nationwide population-based case-control study. *Am J Gastroenterol* 2009; **104**: 96-101 [PMID: 19098856 DOI: 10.1038/ajg.2008.34]
15 **Englesbe MJ**, Schaubel DE, Cai S, Guidinger MK, Merion RM. Portal vein thrombosis and liver transplant survival benefit. *Liver Transpl* 2010; **16**: 999-1005 [PMID: 20677291 DOI: 10.1002/lt.22105]
16 **Maruyama H**, Okugawa H, Takahashi M, Yokosuka O. De novo portal vein thrombosis in virus-related cirrhosis: predictive factors and long-term outcomes. *Am J Gastroenterol* 2013; **108**: 568-574 [PMID: 23381015 DOI: 10.1038/ajg.2012.452]
17 **D'Amico G**, De Franchis R. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. *Hepatology* 2003; **38**: 599-612 [PMID: 12939586]
18 **Augustin S**, Altamirano J, González A, Dot J, Abu-Suboh M, Armengol JR, Azpiroz F, Esteban R, Guardia J, Genescà J. Effectiveness of combined pharmacologic and ligation therapy in high-risk patients with acute esophageal variceal bleeding. *Am J Gastroenterol* 2011; **106**: 1787-1795 [PMID: 21625271 DOI: 10.1038/ajg.2011.173]
19 **Nery F**, Chevret S, Condat B, de Raucourt E, Boudaoud L, Rautou PE, Plessier A, Roulot D, Chaffaut C, Bourcier V, Trinchet JC, Valla DC. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. *Hepatology* 2015; **61**: 660-667 [PMID: 25284616 DOI: 10.1002/hep.27546]
20 **Villa E**, Cammà C, Marietta M, Luongo M, Critelli R, Colopi S, Tata C, Zecchini R, Gitto S, Petta S, Lei B, Bernabucci V, Vukotic R, De Maria N, Schepis F, Karampatou A, Caporali C, Simoni L, Del Buono M, Zambotto B, Turola E, Fornaciari G, Schianchi S, Ferrari A, Valla D. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. *Gastroenterology* 2012; **143**: 1253-1260.e1-4 [PMID: 22819864]
21 **Anstee QM**, Dhar A, Thursz MR. The role of hypercoagulability in liver fibrogenesis. *Clin Res Hepatol Gastroenterol* 2011; **35**: 526-533 [PMID: 21570930]
22 **Lisman T**, Kamphuisen PW, Northup PG, Porte RJ. Established and new-generation antithrombotic drugs in patients with cirrhosis - possibilities and caveats. *J Hepatol* 2013; **59**: 358-366 [PMID: 23548197]
23 **Aldawood A**, Arabi Y, Aljumah A, Alsaadi A, Rishu A, Aldorzi H, Alqahtani S, Alsultan M, Felemban A. The incidence of venous thromboembolism and practice of deep venous thrombosis prophylaxis in hospitalized cirrhotic patients. *Thromb J* 2011; **9**: 1 [PMID: 21244669]
24 **Senzolo M**, M Sartori T, Rossetto V, Burra P, Cillo U, Boccagni P, Gasparini D, Miotto D, Simioni P, Tsochatzis E, A Burroughs K. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. *Liver Int* 2012; **32**: 919-927 [PMID: 22435854]
25 **Amitrano L**, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, Romano L, Balzano A. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. *J Clin Gastroenterol* 2010; **44**: 448-451 [PMID: 19730112]
26 **Delgado MG**, Seijo S, Yepes I, Achécar L, Catalina MV, García-Criado A, Abraldes JG, de la Peña J, Bañares R, Albillos A, Bosch J, García-Pagán JC. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. *Clin Gastroenterol Hepatol* 2012; **10**: 776-783 [PMID: 22289875]
27 **Werner KT**, Sando S, Carey EJ, Vargas HE, Byrne TJ, Douglas DD, Harrison ME, Rakela J, Aqel BA. Portal vein thrombosis in patients with end stage liver disease awaiting liver transplantation: outcome of anticoagulation. *Dig Dis Sci* 2013; **58**: 1776-1780 [PMID: 23314858 DOI: 10.1007/s10620-012-2548-y]
28 **Bechmann LP**, Sichau M, Wichert M, Gerken G, Kröger K, Hilgard P. Low-molecular-weight heparin in patients with advanced cirrhosis. *Liver Int* 2011; **31**: 75-82 [PMID: 20958919 DOI: 10.1111/j.1478-3231.2010.02358.x]
29 **Potze W**, Arshad F, Adelmeijer J, Blokzijl H, van den Berg AP, Porte RJ, Lisman T. Routine coagulation assays underestimate levels of antithrombin-dependent drugs but not of direct anticoagulant drugs in plasma from patients with cirrhosis. *Br J Haematol* 2013; **163**: 666-673 [PMID: 24219333]
30 **Tripodi A**, Chantarangkul V, Mannucci PM. The international normalized ratio to prioritize patients for liver transplantation: problems and possible solutions. *J Thromb Haemost* 2008; **6**: 243-248 [PMID: 17988228]
31 **Trotter JF**, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and model for endstage liver disease (MELD) based on selection of clinical laboratory. *Am J Transplant* 2007; **7**: 1624-1628 [PMID: 17511686]
32 **Tripodi A**, Chantarangkul V, Primignani M, Fabris F, Dell'Era A, Sei C, Mannucci PM. The international normalized ratio calibrated for cirrhosis (INR(liver)) normalizes prothrombin time results for model for end-stage liver disease calculation. *Hepatology* 2007; **46**: 520-527 [PMID: 17659574]
33 **Bellest L**, Eschwège V, Poupon R, Chazouillères O, Robert A. A modified international normalized ratio as an effective way of prothrombin time standardization in hepatology. *Hepatology* 2007; **46**: 528-534 [PMID: 17654598]
34 **Yeh CH**, Hogg K, Weitz JI. Overview of the new oral anticoagulants: opportunities and challenges. *Arterioscler Thromb Vasc Biol* 2015; **35**: 1056-1065 [PMID: 25792448 DOI: 10.1161/ATVBAHA.115.303397]
35 **Steiner T**, Böhm M, Dichgans M, Diener HC, Ell C, Endres M, Epple C, Grond M, Laufs U, Nickenig G, Riess H, Röther J, Schellinger PD, Spannagl M, Veltkamp R. Recommendations for

the emergency management of complications associated with the new direct oral anticoagulants (DOACs), apixaban, dabigatran and rivaroxaban. *Clin Res Cardiol* 2013; **102**: 399-412 [PMID: 23669868 DOI: 10.1007/s00392-013-0560-7]

36 **Ruff CT**, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, Camm AJ, Weitz JI, Lewis BS, Parkhomenko A, Yamashita T, Antman EM. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014; **383**: 955-962 [PMID: 24315724]

37 **van Es N**, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. *Blood* 2014; **124**: 1968-1975 [PMID: 24963045]

38 **Castellucci LA**, Cameron C, Le Gal G, Rodger MA, Coyle D, Wells PS, Clifford T, Gandara E, Wells G, Carrier M. Clinical and safety outcomes associated with treatment of acute venous thromboembolism: a systematic review and meta-analysis. *JAMA* 2014; **312**: 1122-1135 [PMID: 25226478]

39 **Holster IL**, Valkhoff VE, Kuipers EJ, Tjwa ET. New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis. *Gastroenterology* 2013; **145**: 105-112. e15 [PMID: 23470618]

40 **Englesbe MJ**, Kubus J, Muhammad W, Sonnenday CJ, Welling T, Punch JD, Lynch RJ, Marrero JA, Pelletier SJ. Portal vein thrombosis and survival in patients with cirrhosis. *Liver Transpl* 2010; **16**: 83-90 [PMID: 20035521]

41 **John BV**, Konjeti R, Aggarwal A, Lopez R, Atreja A, Miller C, Zein NN, Carey WD. Impact of untreated portal vein thrombosis on pre and post liver transplant outcomes in cirrhosis. *Ann Hepatol* 2013; **12**: 952-958 [PMID: 24114826]

42 **de Franchis R**. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; **63**: 743-752 [PMID: 26047908 DOI: 10.1016/j.jhep.2015.05.022]

43 **Hollingshead M**, Burke CT, Mauro MA, Weeks SM, Dixon RG, Jaques PF. Transcatheter thrombolytic therapy for acute mesenteric and portal vein thrombosis. *J Vasc Interv Radiol* 2005; **16**: 651-661 [PMID: 15872320]

44 **Senzolo M**, Burra P, Patch D, Burroughs AK. Tips for portal vein thrombosis (pvt) in cirrhosis: not only unblocking a pipe. *J Hepatol* 2011; **55**: 945-946; author reply 947-948 [PMID: 21419182 DOI: 10.1016/j.jhep.2011.02.027]

45 **Luca A**, Miraglia R, Caruso S, Milazzo M, Sapere C, Maruzzelli L, Vizzini G, Tuzzolino F, Gridelli B, Bosch J. Short- and long-term effects of the transjugular intrahepatic portosystemic shunt on portal vein thrombosis in patients with cirrhosis. *Gut* 2011; **60**: 846-852 [PMID: 21357252]

P- Reviewer: Denk GU, Tsai WL **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Liu SQ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com