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EDITORIAL

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Pancreatitis-related splanchnic vein thrombosis: What role, what warnings for anticoagulation therapy?

In vascular diseases primarily involving the portal venous system, the mechanistic role of inherited or acquired thrombophilia and the need for long-term anticoagulation treatment are definitely acknowledged, though the risk of portal hypertensive bleeding is a warning. Conversely, in the more frequent secondary involvement of the portal venous system where circumstantial local factors, mainly abdominal inflammatory or expansive lesions are the leading causes, thrombophilia is less relevant. Consequently, there has been no consensus for the indication for anticoagulation in such situations, where both bleeding risk and thrombosis coexist.[1] However, the burden of these disorders is high. Specifically, the incidence of acute pancreatitis, already ranking among the most frequent inpatient gastrointestinal diagnoses in the West, is increasing, alongside the increasing incidence of obesity and cholelithiasis and the unabating incidence of alcohol abuse. Hence, the risk of pancreatitis-related splanchnic vein thrombosis (SVT) is increasing as well.

The Chinese Practice Guidance for the diagnosis and treatment of pancreatitis-related splanchnic vein thrombosis,[2] proposed in a recent issue of this journal, represents the effort of a multidisciplinary team of gastroenterologists, hematologists, interventional radiologists and surgeons to review the current scientific literature and provide expert guidance for this challenging topic. Both acute and chronic pancreatitis are addressed, as both may be complicated by SVT, with the entailed risks of left-sided or, more rarely, full-blown portal hypertension, and of mesenteric ischemia or infarction in case of thrombosis progression. Nonetheless, these disorders also carry a risk of bleeding, either from arterial vessels, mainly the splenic artery or pseudoaneurysms, or venous bleeding, principally from ruptured gastric varices developed as a sequel of splenic vein thrombosis, all carrying an exceedingly high mortality rate. Therefore, the clinical dilemma is whether to treat the SVT with anticoagulants to prevent its sequels (which include bleeding) and further thrombosis progression, or to refrain from treatment, taking into consideration the risk of bleeding, which may be severe, and conceivably even more severe in patients on anticoagulants.

The Practice Guidance looks at such situations and provides good synthesis and is shareable, though it does not contain enough evidence-based clinical statements. Indeed, the heterogeneity of the available studies and the lack of randomized trials preclude performing a meta-analysis or grading the evidence and strength of the recommendations. Thus, the consensus statements are an updated expert guidance but cannot replace a careful clinical judgment of the current emergency situation of bleeding or thrombosis in the individual patient. Here I comment on some of the proposed statements and few additional controversial issues.

A first cluster of questions on acute pancreatitis refer to the effective risk of SVT, its natural history and the effect of anticoagulation treatment. How often does SVT occur in acute pancreatitis? What is the reason for the highly variable reported incidence of 1%-24%?[3-7]

Acute pancreatitis in most cases takes a mild course, where nausea and pain management, fluid infusion and early oral feeding rapidly achieve improvement. Conversely, in its severe form experienced by 20%-30% of patients, acute pancreatitis is a severe disease with high mortality rates.[8] SVT occurs because of pancreatic inflammation or compression by a pseudocyst and is closely associated with the extent and severity of pancreatic necrosis (see Statement 3 in the Practice Guidance). Hence, the quite variable reported incidence of pancreatitis-related SVT probably reflects the different severity of acute pancreatitis evaluated in the available studies. Moreover, some difference also arises from the diverse accuracy of the tools used for diagnosing SVT. Doppler ultrasound is the first-line diagnostic tool, but its accuracy depends on the operator's skill. Furthermore, abdominal gas and fluid accumulation may impede the operator's vision. Computed tomography (CT) or magnetic resonance imaging (MRI) may be necessary to confirm the diagnosis (see Statement 7), with three-dimensional reconstruction as a further appliance for better evaluating the peripancreatic vessels.[9,10] Because of its limited accuracy, Doppler ultrasound could miss splenic vein thrombosis, which is actually the most frequent site of SVT in acute pancreatitis. Therefore, a standardized diagnostic approach is required in acute pancreatitis, and CT or MRI should be performed, unless a Doppler ultrasound can clearly recognize the patency of the peripancreatic vessels, which could be a hard task in acute pancreatitis, particularly if it is moderately severe or severe. Such a systematic approach should be able to lessen the wide range of reported incidence of SVT in acute pancreatitis, improving the definition of the scale of the risk of SVT. Indeed, a more accurate assessment of the SVT rate would be useful in the perspective of assessing risks and benefits of preemptive anticoagulation.

Further questions arise: What is the natural history of SVT? How does anticoagulation influence the outcome of SVT? How does anticoagulation influence the gastrointestinal bleeding risk, either related or unrelated to pancreatitis?

Due to its position close to the body and tail of the pancreas the splenic vein is the vessel most commonly involved in pancreatitis-related SVT, followed by the portal and mesenteric veins[7,11] (see Statement 2). Splenic vein thrombosis often regresses spontaneously after the resolution of pancreatitis[12] but this may not be the rule in severe disease. Instead, it may persist and cause left-sided portal hypertension or even progress, involving the portal or the mesenteric veins, possibly causing full-blown portal hypertension or, if it involves the superior mesenteric vein roots deeply, intestinal ischemia or infarction. Unfortunately, we are not able to identify early on which patients with pancreatitis-related acute splenic vein thrombosis will develop spontaneous recanalization and which will progress to bowel ischemia or portal hypertension.

The Practice Guidance suggests watchful waiting in patients with splenic vein thrombosis (ie, not to start anticoagulation, but to monitor closely the progression, persistence or regression of the splenic vein thrombosis) and to start anticoagulation in case of thrombosis extension (see Statement 8). However, the outcome of anticoagulation therapy for acute pancreatitis-related SVT is not particularly good. In fact, the rate of SVT recanalization is as low as 14%, similar to the 11% rate achieved in the absence of anticoagulation therapy.[13] Hence, as anticoagulation after SVT occurrence is barely effective in achieving recanalization, the question whether anticoagulation should be implemented before the occurrence of SVT in acute pancreatitis becomes more acute. Although there have been no randomized controlled trials on anticoagulants in acute pancreatitis, the progression of SVT is deemed to require anticoagulation treatment, as an attempt at preventing intestinal infarction or the development of a portal cavernoma and its ensuing long-standing portal-hypertensive sequels. Nonetheless, bleeding in severe acute pancreatitis is a major cause of morbidity and mortality. There is no clear evidence that anticoagulation may increase the risk or lethality of bleeding, but this looks plausible. Though the bleeding risk is, in general, lower than the risk of SVT, in certain situations, such as the occurrence of pseudocysts complicated by pseudoaneurysm formation, the risk of bleeding is reasonably perceived as being too high and anticoagulation is contraindicated.[14] Furthermore, anticoagulation treatment may be contraindicated in patients with severe portal hypertension complications, especially those with a recent history of gastrointestinal bleeding. Indeed, the time elapsing from splenic vein occlusion to the development of left-sided portal hypertension may be short. Moreover, in the case of extended thrombosis of the portal venous system, which demands the initiation of anticoagulation treatment, an endoscopic assessment of the presence and size of gastric or esophageal varices is mandatory (see Statement 7). Bleeding from gastric varices require prompt endoscopic treatment with the injection of tissue glue, and bleeding from esophageal varices requires band ligation. The indication of anticoagulation treatment in such cases could be deferred, as the rebleeding risk is non-negligible. In addition, the finding of huge, though non-bleeding gastric varices at endoscopy raises the question whether to start anticoagulation or not. In the setting of portal hypertension due to cirrhosis, neither the bleeding risk nor the rate of recurrent bleeding during the course of esophageal band ligation appears to be higher in patients on anticoagulants than untreated patients.[15] However, in gastric varices associated with left-sided portal hypertension in pancreatitis the matter is different. Though gastric variceal bleeding can occur irrespective of anticoagulation treatment, its severity could be higher in patients on anticoagulants. Thus, such treatment could be unwise in patients with SVT-related pancreatitis and recent gastric variceal bleeding or who are having ongoing endoscopic treatment for gastric varices. On the other hand, starting anticoagulation after the complete treatment of gastric varices could be useless, as the longer the time lapse from SVT and the start of anticoagulation treatment, the lower the probability of recanalization of the splenic vein and the regression of left-sided portal hypertension.[16] Overall, it is quite clear that a straightforward indication in favor (or against) anticoagulation treatment is not always feasible.

Which anticoagulant, which dosage and how long it should be given are further relevant questions. However, in the early setting of severe or moderately severe acute pancreatitis, the oral route is unsuitable and unfractionated heparin or low-molecular-weight heparin (unless there is renal insufficiency) are likely to be appropriate. Whether heparin, at a prophylactic rather than a therapeutic dosage, may be adequate and safe in treating SVT progression requires performing a prospective study. A subsequent transition to vitamin K antagonists is questionable. Direct oral anticoagulants, though more versatile than vitamin K antagonists and promising in this clinical situation, still lack easily available antidotes for prompt rescue in case of bleeding, and are not licensed yet for such an indication. As pancreatitis is not a permanent prothrombotic condition, the Practice Guidance suggests that the duration of anticoagulation therapy should not exceed 3-6 months. This is likely to be adequate, even in the presence of some form of thrombophilia that, although commonly found in patients with pancreatitis, has no pathophysiological role in pancreatitis-related SVT, which is mainly caused by local inflammation, and should not be systematically searched for.[17]

Beside the time lapse from the occurrence of SVT, the size of gastric varices, whether the pancreatitis is acute or chronic and the extent of thrombosis of the portal venous system are among the variables to consider when facing the challenging decision of prescribing or not prescribing anticoagulants to a patient with pancreatitis-related SVT. A recent splenic vein thrombosis could be treated with short-acting anticoagulants, ie, unfractionated heparin, with close monitoring of both SVT on imaging and gastric varices at endoscopy. Conversely, an established left-sided portal hypertension due to long-standing splenic vein thrombosis in chronic pancreatitis will not benefit from anticoagulation. In such a case, and only if needed due to gastric variceal bleeding, a splenectomy is curative (see Statement 11), though technically challenging or even impossible in some patients with chronic pancreatitis with extensive peripancreatic fibrosis or pancreatic pseudocysts, thus requiring both a splenectomy and resection of the pancreatic body and tail.

A last question refers to the possible role of preemptive anticoagulation in acute pancreatitis. In its severe form, acute pancreatitis is an extremely acute disease associated with prolonged

immobilization, and entails a risk for venous thromboembolism in general, not only for SVT. Pancreatitis-related SVT, mainly involving the splenic vein, is the direct consequence of acute or chronic inflammatory processes of the pancreas. Although coagulation derangement, as measured by raised D-dimer levels, is frequently observed, it is often mild, whereas overt disseminated intravascular coagulation involving both diffuse bleeding and thrombotic diathesis is rare. Thrombophilia, though frequently identifiable if searched for, does not appear to play a relevant role in the pathophysiology of pancreatitis-related SVT, which appears to be the direct consequence of the inflammatory processes of the pancreas. Thus, should we treat our patients with acute pancreatitis preemptively with anticoagulants in order to avoid SVT and general venous thromboembolism as well? Conversely, should we refrain from anticoagulation, as these patients are also at a high risk for severe gastrointestinal bleeding? The APACHE II score, the Ranson score and the Balthazar CT severity index predict the severity of pancreatitis and the risk of pancreatitis-related SVT as well.[18-20] However, these predictors of severity are also associated with the risk of bleeding. In severe or moderately severe acute pancreatitis, and even more in the presence of further risk factors for SVT, such as chronic alcohol use, male gender and smoking, the option of preemptive, low-dose anticoagulation, ie, unfractioned heparin, should be considered. However, this is an opinion, as no studies addressing the risk: benefit ratio of such an approach exist and a prospective, possibly randomized study is needed. The Practical Guidance cannot tackle this topic, as no recommendation can currently be delivered. However, the proposal to stratify the risk by applying the current predictors of pancreatitis-related SVT (see Statement 4) would prompt future prospective collaborative studies to determine whether preemptive anticoagulation can safely prevent SVT in acute pancreatitis, without increasing bleeding risk or bleeding-related mortality.

In summary, the Chinese Practice Guidance for the diagnosis and treatment of pancreatitis-related splanchnic vein thrombosis presents the current scientific evidence and provides expert guidance to navigate this critical condition. Some of the issues outlined here cannot be translated into clear-cut clinical decisions and require a case-by-case evaluation, entailing an accurate assessment of the potential risks and benefits of anticoagulation in critical patients, prone either to potentially fatal bleeding or progressive, severely incapacitating or lethal SVT. As with all evolving topics, several issues remain unclear. Thus, some statements will help the reader to focus on the problems, rather than providing conclusive recommendations. In such instances, the Practice Guidance is a valuable tool to standardize the clinical approach and endorse homogeneous, collaborative studies able to generate robust evidence, which we hope may be available in the near future.

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