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WORD COUNT	3874	TIME SUBMITTED	23-APR-2023 03:56PM
		PAPER ID	99000370

Current opinions on the use of therapeutic anticoagulation for splanchnic vein thrombosis in acute pancreatitis: A survey and case-vignette study in the Netherlands

Sissingh NJ *et al*. Anticoagulation for pancreatitis-induced splanchnic vein thrombosis

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INTRODUCTION

Acute pancreatitis is an inflammatory disorder of the pancreas and is self-limiting in the majority of patients[1,2]. However, approximately 20% of patients develop a moderate or severe disease course, with (peri) pancreatic necrosis and collections[3,4]. Due to the combination of local inflammation and mechanical compression, these complications may cause thrombus formation in the splanchnic circulation, including the portal, splenic and superior mesenteric vein[5,6]. The reported estimates on the incidence of splanchnic vein thrombosis (SVT) in acute pancreatitis range from 17% to 23%, and are even higher in complicated acute pancreatitis[7,8]. The clinical presentation of SVT varies between an asymptomatic thrombus to potential lethal complications, such as portal or left side hypertensive bleeding and small bowel ischemia[9-11]. For this reason, early treatment with therapeutic anticoagulation is recommended in patients with acute SVT[12-14]. However, consistent evidence to drive this decision in acute pancreatitis patients does not exist[15-18]. In fact, a recent meta-analysis from our study group showed that 53% of acute pancreatitis patients do not receive therapeutic anticoagulation[15]. This proportion of untreated patients is substantially higher than previously reported in other SVT populations[19], probably because of the fear of serious bleeding. Variation in clinical practice also became apparent in this meta-analysis[15], as anticoagulation use and the type of agent used were very heterogeneous between

studies. Therefore, the aim of this survey was to gain more insight into current opinions of pancreatologists on anticoagulation therapy for SVT following acute pancreatitis.

MATERIALS AND METHODS

We conducted an online national survey and case vignette study among members of the Dutch Pancreatitis Study Group (DPSG) and the Dutch Pancreatic Cancer Group (DPCG). Members were excluded if they were not primary care-takers in the treatment of patients with AP (*e.g.*, radiologists, oncologists, basic scientists). The survey was built in Research Electronic Data Capture, and invitations to participate were sent by e-mail in November 2021, followed by four weekly reminders. Additionally, the survey was promoted through newsletters and during annual study group meetings of the DPSG and DPCG.

Survey design

The survey was developed by a multidisciplinary team of surgeons, gastroenterologists, and radiologists, and included 3 demographical questions, 17 general questions and 3 case vignettes (supplementary material). Demographic information included the responders' specialty, type of hospital and working experience. The general questions focused on treatment of SVT and potential factors that may influence the responders' decision. The case-vignettes addressed the preferred treatment strategy in different clinical cases at different time points. All cases however, concerned a 50-year-old male patient with acute alcoholic necrotising pancreatitis, and can be summarized as follows.

Case vignette 1: A patient visited the emergency department, 5 d after onset of abdominal pain. Contrast-enhanced CT (CECT) showed necrotising pancreatitis with acute necrotic collection in the head of the pancreas (Figure 1A) and: A1: Luminal narrowing of the portal vein without the presence of collateral circulation (Figure 1B); A2: Intraluminal filling defect in the portal vein without the presence of collateral

circulation; A3: Intraluminal filling defect in the portal vein without the presence of collateral circulation + a pseudoaneurysm in the proximal splenic artery (Figure 1C).

Case vignette 2: A patient admitted to the ward, 14 d after onset of abdominal pain. The patient showed signs of clinical detoriation with fever and rising inflammatory parameters. The CECT showed almost fully encapsulated pancreatic necrosis without gas configurations (Figure 1D) and a new intraluminal filling defect in the portal vein without the presence of collateral circulation (Figure 1E). The diagnosis of suspected infected pancreatic necrosis was made.

Case vignette 3: A homeless patient visited the emergency department, 30 d after onset of vague abdominal pain. CECT showed necrotising pancreatitis and: CA: Intraluminal filling defect in the portal vein with the presence of collateral circulation; CB: Thrombus progression and expansion of the collateral circulation (Figure 1F); The threshold to assume group agreement was set at 75%. If a question ranged from always, usually, sometimes and never, agreement was defined when 75% of the pancreatologists rated it as always or usually (regularly), or sometimes and never (infrequently).

Definitions

SVT was predefined as an actual intraluminal filling defect on imaging of one or more of the splanchnic veins. The chronicity was divided into (sub)acute thrombosis or chronic thrombosis (with concomitant collaterals), anatomical location into portal, splenic and/or superior mesenteric vein, degree into a total or partial occlusion and extent into an isolated thrombus or a thrombus in several venous segments. Thrombus progression was defined as progression into other splanchnic vein(s), into total occlusion, or both.

Statistical analysis

Descriptive data are presented as counts with proportions for categorical data. All analyses were performed using IBM SPSS (20).

RESULTS

A total of 93 of the 139 invited pancreatologists (67%) responded and participated in this survey and case vignette study; 67 gastroenterologists (72%), 25 surgeons (27%) and 1 intensivist (1%). The majority worked in a non-academic centre (70%) and had more than 10 years of experience in treating AP patients (60%). Demographic characteristics are presented in Table 1.

Indications for and details of treatment with therapeutic anticoagulation

Agreement was reached on whether therapeutic anticoagulation should be prescribed for SVT and luminal narrowing of one or more of the splanchnic veins in acute pancreatitis patients. For SVT, therapeutic anticoagulation was regularly prescribed by 71 (76%) and infrequently by 22 (24%) pancreatologists. In case of luminal narrowing, therapeutic anticoagulation was only regularly prescribed by 12 (13%) pancreatologists. Avoiding complications, such as portal hypertension and bowel ischemia, was the main reason for 81 pancreatologists (87%) to start therapeutic anticoagulation. Screening for an underlying prothrombotic disorder in patients diagnosed with SVT was regularly performed by 14 (15%) pancreatologists, only in patients with a history of one (or more) thrombotic events by 40 (43%), and infrequently by 39 (42%) pancreatologists. There was agreement on the preferred initial type of therapeutic anticoagulation for SVT 81 pancreatologists (87%) preferred subcutaneous low-molecular-weight heparin (LMWH)], but not on the preferred follow-up type. Imaging after the index admission was chosen as follow-up strategy by 79 pancreatologists (85%). Thirteen pancreatologists (13%) indicated that they usually stop anticoagulant therapy in case of achieved radiological recanalization, 35 (38%) after a period of 3 mo, 42 (45%) after 6 mo, and 3 (3%) after 12 mo. All details are provided in Table 2.

Determinants of prescribing therapeutic anticoagulation

Seventy-eight pancreatologists (84%) have chosen the time course of thrombosis as the most important factor supporting anticoagulant therapy; 84 pancreatologists (90%) prescribe therapeutic anticoagulation in case of a (sub)acute thrombosis *vs* 9 (10%) for both (sub)acute and chronic thrombosis. Moreover, 70 pancreatologists (76%) have chosen portal vein thrombosis as the most preferred location to initiate therapeutic anticoagulation, whereas splenic vein thrombosis was chosen as least preferred location by 80 pancreatologists (86%). The majority of pancreatologists (85%) treat both total and partial occlusive thrombosis. There was no agreement whether the risk of different types of bleeding should be considered as a major barrier to prescribe therapeutic anticoagulation. The need for invasive interventions for local complications of acute pancreatitis influenced the decision whether or not to initiate anticoagulation therapy in about half of pancreatologists (52%). All details are outlined in Table 3.

Statements on prognosis

An association between the presence of SVT and worse clinical outcomes in patients with acute pancreatitis was assumed by 67 pancreatologists (72%) (Figure 2). Moreover, the vast majority (88%) agreed that therapeutic anticoagulation for splanchnic vein thrombosis improves clinical outcomes in these patients. Insufficient evidence was the most frequently quoted reason among pancreatologists who disagreed with this second statement.

Case-vignettes

The results of the case vignettes are summarized in Figure 3. In the first case vignette (patient 1, day 5 of acute necrotising pancreatitis), 11 pancreatologists (12%) would prescribe a therapeutic dose anticoagulation if luminal narrowing without collateral circulation was detected in the portal vein. Of the 82 pancreatologists (88%) who opted for no therapeutic dose anticoagulation, 73 (89%) would change treatment strategy in case an actual filling defect in the portal vein was detected. In total, 84 pancreatologists

(90%) would prescribe therapeutic dose anticoagulation to this patient with an actual portal vein thrombosis without collateral circulation. If a pseudoaneurysm was concomitantly present, 43 of those 84 pancreatologists (51%) who favoured a therapeutic dose anticoagulation would switch to a prophylactic dose anticoagulation (n = 28, 65%) or no anticoagulation at all (n = 15, 35%), leaving 41 pancreatologists (44%) in the therapeutic anticoagulation group.

In the second case vignette (patient 2, day 14 of suspected infected necrotising pancreatitis), 77 pancreatologists (82%) would prescribe therapeutic dose anticoagulation if a portal vein thrombosis without collateral circulation was detected. The presence of (suspected) infected pancreatic necrosis influenced the choice of anticoagulation agent in 49 pancreatologists (52%). Almost all of these pancreatologists pointed out that once infected pancreatic necrosis is suspected, they would choose an agent with a short half-life because of the potentially need of invasive intervention.

In the third case vignette (patient 3, day 30 of acute necrotising pancreatitis), 44 pancreatologists (47%) would prescribe a therapeutic dose anticoagulation if a portal vein thrombosis with collateral circulation was detected. Of these 44 pancreatologists, 19 (43%) would perform upper endoscopy to screen for and-if present-treat oesophageal varices before starting anticoagulation therapy. In case of thrombus progression (extension of the thrombus to the splenic vein and expansion of the collateral pathway), 11 pancreatologists (12%) would stay conservative (*i.e.*, no therapeutic dose of anticoagulation), 82 (88%) would start or continue a therapeutic dose anticoagulation and none would proceed to an intervention.

DISCUSSION

This first nationwide survey and case vignette study gives insight into the clinical scenarios in which therapeutic anticoagulation is currently used, and not used to treat or prevent splanchnic vein thrombosis in acute pancreatitis patients. In an earlier study[15], we found 7 retrospective cohort studies evaluating therapeutic anticoagulation in this patient category with conflicting results in clinical outcome[20-27]. These studies

were of moderate quality and therefore the pancreatologist' preference and belief predominate in current decision making rather than scientific evidence.

An important finding of the current study was that more than 75% of pancreatologists regularly prescribe therapeutic anticoagulation for SVT, particularly for a thrombus that acutely developed. This is in line with recommendations from general guidelines for SVT management[12-14]. In the absence of a visualized thrombus, most pancreatologists indicated not to treat compressed veins with anticoagulation. Although wall shear stress in a compressed vessel may promote platelet activation, and subsequently thrombus formation[28], there is no data yet to question the opinion of the pancreatologists.

In this study, the most important reason to administer therapeutic anticoagulation was to avoid complications including bowel ischemia and portal hypertension. Bowel ischemia has been reported in up to 33% of acute pancreatitis patients treated with therapeutic anticoagulation *vs* 16% of untreated patients[22,24,25]. A potential explanation for this discrepancy could be that bowel ischemia was already present prior to the start of therapy, therefore being an indication for therapeutic anticoagulation rather than a consequence. In addition, the presence of varices and other collaterals have been equally reported[15], and only one of the aforementioned studies described one case of bleeding from oesophageal varices in an anticoagulated patient[24]. Again, it is likely that a perceived bleeding risk influenced the decision whether or not to prescribe therapeutic anticoagulation. This confounding by indication clearly limits the interpretation of these retrospective studies.

Achieving vessel recanalization was chosen as the second goal. A recent meta-analysis showed that the pooled rate of recanalization of SVT was similar between treated (36%) and untreated patients (31%)[15]. However, there is reason to believe that the benefit of anticoagulation therapy may alter when considering the anatomical location of the thrombosis[21,29]. Patients with portal vein or superior mesenteric vein thrombosis may have an increased risk of complications, while having lower spontaneous recanalization rates. In particular, mortality rates of patients with superior

mesenteric vein thrombosis are reported up to 50%[30,31]. On the other hand, splenic vein thrombosis, which is by far the most common site of thrombosis in acute pancreatitis patients, forms a less serious concern for gastrointestinal bleeding and insufficient recanalization[8,26,32]. A selective anticoagulation policy, in which therapeutic anticoagulation was reserved for portal- and superior mesenteric vein thrombosis, was recently assessed in a retrospective study[33]. This study showed a recanalization rate of 67% in portal- and superior mesenteric vein thrombosis, which is substantially higher than previously reported[15]. In addition, a recent practice guideline from the Pancreas study group, Chinese Society of Gastroenterology, recommends a selective anticoagulation policy[34]. In this survey, portal vein thrombosis, followed by superior mesenteric vein thrombosis, was also the pancreatologists' preferred location for prescribing therapeutic anticoagulation, while splenic vein was the least preferred location.

With respect to chronic SVT, the current guidelines do not recommend therapeutic anticoagulation[10]. This is in line with the reported use in case vignette C, with the exception of the case of the patient with thrombus progression and expansion of the collateral circulation. In this scenario, 88% of pancreatologists would treat such patient with therapeutic anticoagulation. A recent multicentre randomised controlled trial comparing daily rivaroxaban 15 mg/d to no anticoagulation in patients with noncirrhotic chronic portal vein thrombosis[35], formally challenged the guideline recommendations. This study showed that rivaroxaban, even in prophylactic dose, reduced the incidence of venous thromboembolism; therefore, this study may initiate a shift towards a more frequent use of anticoagulation in chronic SVT. On that note, primary prophylaxis of portal hypertensive bleeding should be performed, as laid out by the BAVENO IV guideline[13]. In this survey, however, the minority of pancreatologists followed this recommendation. Improvements should also be made to distinguish acute from chronic SVT. Currently, no clear definition for chronic SVT exists other than a presumed time course of more than 6 mo or the presence of multiple small collaterals around the obstructed veins[10,36], which is not useful to diagnose a

nonocclusive chronic thrombosis (*i.e.*, absence of collateral pathways). A promising invention to overcome this problem is magnetic resonance noncontrast thrombus imaging, though validation is still needed[37].

According to our survey, subcutaneous LMWH was the favoured initial type of therapeutic anticoagulation, while no agreement regarding the choice of long-term anticoagulation and its duration was found. In current guidelines, switching LMWH to a vitamin K antagonist once reaching the target range is the reported strategy for patients with SVT[12-14,38]. The use of direct oral anticoagulation (*i.e.*, apixaban) in acute pancreatitis patients with SVT is reported in two studies and showed comparable results[21,33]. However, in the case of (suspected) infected pancreatic necrosis, LMWH seems to be preferred by more than half of the pancreatologists, due to its short half-life and reversibility. Besides, many acute pancreatitis patients have reduced caloric intake limiting the absorption of DOACS. Therefore, it seems fair to advise LWMH, especially in the acute phase. Looking at the duration of anticoagulation therapy for provoked SVT in patients with a transient risk factor, such as acute pancreatitis, the suggested duration is 3 mo to 6 mo[12-14,38]. Consistently, 38% and 45% of the pancreatologists in our survey preferred 3 mo and 6 mo treatment duration, respectively.

Based on the available literature, it remains unclear whether therapeutic anticoagulation is associated with higher rates of bleeding. An increased bleeding risk with therapeutic anticoagulation has been reported up to 33% of patients[21,25,26], but there are also studies showing lower rates of bleeding[24]. The theory for this latter finding is that therapeutic anticoagulation prevents thrombus progression, therefore reducing the portal pressure and consequently the risk of bleeding[19]. In this study, the risk of bleeding was not identified as a significant discouraging factor, as only about half of the pancreatologists considered bleeding in general and bleeding related to pseudoaneurysm as a major barrier to prescribe therapeutic anticoagulation. Also, the possible need for invasive intervention, due to suspected infected necrosis, did not significantly influence the treatment strategy. Another critical question is whether SVT influences the disease course of acute pancreatitis patients, but again this remains

unanswered[15]. In this survey, the majority of pancreatologists assumed that the occurrence of SVT is associated with worse clinical outcomes, and interestingly, even more pancreatologists were convinced that the use of therapeutic anticoagulation leads to improved patient outcomes.

A strength of this study is the response rate of 67%, which is relatively high compared to previous surveys among pancreatologists[39-41]. Furthermore, the ratio of 30:70 between academic and non-academic pancreatologists attributed to a valuable insight into the pancreatologists' opinions on the use of therapeutic anticoagulation. This study also has several limitations. First, the results may not directly reflect the actual practice in other countries as only members of two Dutch associations of pancreatology were invited. This decision was made to avoid selection based on publication record, and consequently include pancreatologists who are not actively involved in the treatment of acute pancreatitis[40]. Another advantage of our method is that it allowed us to calculate the survey's response rate by bypassing the confidentiality of membership lists of international pancreatic associations. Second, the clinical presentation of SVT is very heterogeneous, as well as the patient characteristics and clinical disease course among acute pancreatitis patients, which influences current decision making. For this reason, it might have been difficult for pancreatologists to answer some of the general questions. Therefore, case vignettes were used to explore what considerations underpin their decisions. As the descriptions throughout the case vignettes were consistently formulated and only one clinical detail was changed at a time, treatment of patients with superior mesenteric vein and splenic vein thrombosis was not assessed in the case vignettes. Consequently, the pancreatologists' preference on this manifestation of SVT in acute pancreatitis remained unknown. Finally, the rationale behind the "nonprescribing trend" was not assessed adequately, which could be a focus for future research.

CONCLUSION

In conclusion, this national survey demonstrates the tendency of pancreatologists to prescribe therapeutic anticoagulation for acute thrombosis, in particular for acute portal vein thrombosis and in case of thrombus progression, irrespective of the presence of infected necrosis. With therapeutic anticoagulation, the majority of pancreatologists believed that the clinical outcomes of acute pancreatitis patients with splanchnic vein thrombosis will improve. Furthermore, this study reflects on several knowledge gaps in literature, and sets out clear points for future research. Specifically, a deeper understanding of the pathophysiology and natural course of splanchnic vein thrombosis secondary to acute pancreatitis would allow us to clarify the therapeutic role of anticoagulation.

Figure Legends

Figure 1 Imaging findings of case vignette. A: Acute necrotic collection in the head of the pancreas in case vignette 1; B: Luminal narrowing of the portal vein without the presence of collateral circulation in case vignette 1; C: Pseudoaneurysm in the proximal splenic artery in case vignette 1; D: Almost fully encapsulated pancreatic necrosis without gas configurations in case vignette 2; E: Luminal filling defect in the portal vein without the presence of collateral circulation in case vignette 2; F: Extension of the thrombus to the splenic vein (arrow pointing upwards) and expansion of the collateral pathway in the gastroepiploic veins along the great curvature of the stomach (arrow pointing downwards) in case vignette 3.

Figure 2 Statements on prognosis. A: Splanchnic vein thrombosis is associated with worse clinical outcomes; B: Therapeutic anticoagulation improves clinical outcomes. AC: Anticoagulation; SVT: Splanchnic vein thrombosis.

Figure 3 Case vignettes results: Choice of treatment. AC: Anticoagulation.

Table 1 Details of respondents

Demographics	*n* = 93 (%)
Specialty	
Surgeon	25 (27%)
Gastroenterologist	67 (72%)
Intensivist	1 (1%)
Type of hospital	
Academic	28 (30%)
Non-academic, teaching hospital	60 (65%)
Non-academic, non-teaching hospital	5 (5%)
Experience in treating patients with acute pancreatitis	
0-5 years	10 (11%)
5-10 years	27 (29%)
10-15 years	17 (18%)
15-20 years	23 (25%)
> 20 years	16 (17%)

Table 2 Survey results: Indication for and details of treatment with therapeutic anticoagulation

Item	Total (*n* = 93)
Do you prescribe therapeutic AC in case of detected thrombosis in one (or more) of the splanchnic veins?	
Always	23 (25%)
Usually	48 (52%)
Sometimes	21 (23%)
Never	1 (1%)
Do you prescribe therapeutic AC in case of detected luminal narrowing of one (or more) of the splanchnic veins?	
Always	3 (3%)
Usually	9 (10%)
Sometimes	29 (31%)
Never	52 (56%)
Main reason(s) to start therapeutic AC (multiple answers were possible)	
To achieve vessel recanalization	52 (56%)
To avoid complications	81 (87%)
To prevent formation of altered venous anatomy	31 (33%)
To prevent recurrence of SVT	27 (29%)
To prevent another venous thromboembolism	30 (32%)
Other reason[1]	1 (1%)
Do you screen for an underlying prothrombotic disorder?	
Always	2 (2%)
Usually	12 (13%)
Sometimes	25 (27%)
Only in patients with a history of one (or more) thrombotic events	40 (43%)
Never	14 (15%)

Which initial type of therapeutic AC do you prefer?	
(Low molecular weight) heparin subcutaneous	81 (87%)
Unfractionated heparin intravenous	4 (4%)
Direct oral anticoagulation	3 (3%)
Vitamin K antagonist	4 (4%)
Platelet aggregation inhibitor	1 (1%)
Urokinase/ recombinant tissue plasminogen activator	0
Which follow-up type of therapeutic AC do you prefer?	
(Low molecular weight) heparin subcutaneous	9 (10%)
Unfractionated heparin intravenous	0
Direct oral anticoagulation	53 (57%)
Vitamin K antagonist	29 (31%)
Platelet aggregation inhibitor	2 (2%)
Urokinase/ recombinant tissue plasminogen activator	0
Do you generally follow-up SVT after index admission?	
Yes, clinically only	5 (5%)
Yes, with imaging	79 (85%)
No	9 (10%)
After how long do you usually stop the therapeutic AC?	
In case of achieved radiological recanalization	13 (14%)
3 mo	35 (38%)
6 mo	42 (45%)
12 mo	3 (3%)
Never	0

[1]In free text: expansion of thrombosis.

AC: Anticoagulation; SVT: Splanchnic vein thrombosis.

Table 3 Survey results: Determinants of prescribing therapeutic anticoagulation

Item	Total (n = 93)
Do you consider of ... the thrombosis as an important factor to prescribe therapeutic AC? (multiple answers were possible)	
Age (acute or chronic)	78 (84%)
Anatomical location (portal, splenic or superior mesenteric vein)	42 (45%)
Degree (total or partial)	45 (48%)
Extent (isolated thrombosis or thrombosis in several segments)	49 (53%)
Progression (over time)	40 (43%)
When do you prescribe therapeutic AC? In case of:	
(Sub)acute thrombosis	84 (90%)
Chronic thrombosis	0
Both	9 (10%)
Rank the anatomical location of the thrombosis from most likely to less likely to start therapeutic AC:	
Portal vein-splenic vein-superior mesenteric vein	9 (10%)
Portal vein-superior mesenteric vein-splenic vein	61 (66%)
Splenic vein-portal vein-superior mesenteric vein	0
Splenic vein-superior mesenteric vein-portal vein	1 (1%)
Superior mesenteric vein-portal vein-splenic vein	19 (20%)
Superior mesenteric vein-splenic vein-portal vein	3 (3%)
When do you prescribe therapeutic AC? In case of:	
Total thrombosis	9 (10%)
Partial thrombosis	5 (5%)
Both	79 (85%)
Do you consider the risk of ... as a major barrier to prescribe therapeutic AC? (multiple answers were possible)	
Bleeding in general	52 (56%)
Bleeding related to portal hypertension	17 (18%)
Bleeding related to pseudoaneurysm	49 (53%)

Other risk	1 (1%)
Does the need for invasive interventions for local complications of acute pancreatitis influence your decision regarding AC therapy?	
Yes	48 (52%)
No	45 (48%)

*In free text: CVA bleeding history.

AC: Anticoagulation; SVT: Splanchnic vein thrombosis.

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