Acute pancreatitis: from treatment to prevention

Sissingh, N.J.

CHAPTER 10

General discussion and future perspectives

GENERAL DISCUSSION

Acute pancreatitis is a major burden in the Western world. As its incidence has increased significantly over the years and continues to rise, the incidence of both necrotizing pancreatitis and recurrent acute pancreatitis is also expected to increase. Necrotizing pancreatitis carries the risk of complications such as infected necrosis and splanchnic vein thrombosis, whereas each recurrent attack has the potential for the development of necrotizing pancreatitis. To break this vicious cycle, it is of paramount importance to optimize the clinical management of acute pancreatitis. The aim of the studies described in this thesis was to improve strategies *'from treatment to prevention'*.

PART I – TREATMENT OF INFECTED NECROTIZING PANCREATITIS

After antibiotics, the next indicated step in the treatment of infected necrotizing pancreatitis is catheter drainage (1). The goal is to eradicate the source of infection, but the best time to do so has long been debated (2). The POINTER trial recently showed that delayed drainage offers short-term benefits compared with immediate drainage, but its effect on long-term clinical outcomes remained uncertain.

As discussed in **Chapter 2**, the long-term follow-up results of the POINTER trial showed that the following benefits of delayed drainage persisted after more than 4 years of follow-up. First, fewer pancreatic interventions were performed in patients treated with a delayed drainage strategy. Second, the need for intervention was avoided in more than one-third of these patients. Finally, the delayed drainage strategy was not associated with increased with long-term mortality, morbidity, or complications such as recurrent pancreatitis, pancreatic insufficiency, and impaired quality of life. These results were consistent with a recent meta-analysis that included the original POINTER trial and six other studies (3). However, all but one of these studies were retrospective and lacked long-term follow-up (4-9). Nevertheless, we show that a follow-up period of ~2 years seems appropriate for future studies. All POINTER participants had their first drainage procedure, if needed, within 22 months after randomization. Although this is the first long-term cohort study based on prospective randomized data, our results should be considered with some limitations. The majority of patients did not have organ failure at randomization. Some patients were excluded because the treating physician decided that delayed drainage was not feasible. This may have led to an overestimation of the treatment effect of the delayed drainage strategy. Preliminary results from a pilot study showed a beneficial trend for immediate drainage when initiated on the basis of persistent organ failure (10). A full

randomized controlled trial is needed to provide definitive results. Furthermore, the indication for (additional) interventions was not standardized. In the Netherlands, however, guidance on interventions is generally provided by our expert panel system (11). The results of this study provide additional guidance on when to intervene. The starting point is an initial antibiotic-only approach, where the effect of antibiotics can be safely awaited if there is subsequent clinical improvement. This approach offers the opportunity to avoid and reduce the number of invasive procedures.

Future perspectives

An important direction for future research in infected necrotizing pancreatitis is the optimization of antibiotic treatment. Especially as we have shown that treatment is moving towards an even more conservative approach with antibiotics. Currently, there are concerns about the overuse and misuse of antibiotics in patients with (infected) necrotizing pancreatitis. Overuse because antibiotics are often started early in the course of the disease and/or without evidence of infection (12-14). In addition, antibiotics, often broad-spectrum, are continued for long periods of time because the duration of treatment has not yet been standardized (12). And misuse, because microbiological cultures are not always consistent with antibiotic use or are not obtained (12). Routine fine needle aspiration has the potential to overcome the latter (15). Another emerging strategy is antibiotic stewardship programs. These programs address the optimal type, dose, and duration of antibiotic treatment and have been shown to reduce both length of hospital stay and antibiotic resistance. (16-18) The upcoming PIANO trial within the Dutch Pancreatitis Study Group (DPSG) will provide useful data on the implementation of an antibiotic stewardship, including recommendations on when to obtain cultures, in our study population.

In an ideal world, improved antibiotic therapies would eliminate the need for invasive procedures. However, we are not there just yet. The endoscopic step-up approach is now the preferred method (19), so innovation in this area is of great value. In addition to conventional endoscopic drainage and necrosectomy techniques, there are several innovations worth exploring. Placement of a nasocystic tube alongside the transmural stent(s) may be useful to facilitate continuous irrigation of necrotic debris (20). Such a tube may also allow irrigation of necrotic collections with hydrogen peroxide or antibiotics. Hydrogen peroxide may aid in the removal of necrotic debris through the release of oxygen (21, 22). Local administration of antibiotics has the advantage of delivering high concentrations directly to the site of infection (23, 24). The EndoRotor, an automated tissue resection device, could potentially reduce the duration of necrosectomy procedures (25, 26). The latter innovation is now being evaluated in the randomized RESOlVE trial of the DPSG.

As this thesis goes '*from treatment to prevention*', drawing attention to strategies aimed at preventing the risk of a severe disease course is key. Intravenous omega-3 fatty acids ('fish oil') and oral tributyrin (a butyrate prodrug) are promising early-phase agents. Omega-3 fatty acids are known inducers of anti-inflammatory cytokines (27), and may therefore reduce the systemic inflammatory response underlying necrotizing pancreatitis (28, 29). The prophylactic potential of butyrate, a short-chain fatty acid produced by the gut microbiota itself (30), may target bacterial translocation from the gut (31), which is thought to be responsible for the infection of necrosis (32). The hypothesis that both strategies improve clinical outcomes is currently being tested in the DPSG's Phase III PLANCTON trial and the Phase IIa PARROT trial.

PART II – SPLANCHNIC VEIN THROMBOSIS IN ACUTE PANCREATITIS

Therapeutic anticoagulation for splanchnic vein thrombosis aims to prevent bowel ischemia and promote vessel recanalization. Recanalization, in turn, helps to reduce splanchnic hypertension and the risk of bleeding (33). However, its current role in acute pancreatitis remained unclear (34, 35).

To address this, we conducted a systematic review and meta-analysis of the available literature. In **Chapter 3,** we analyzed and presented the combined results of seven retrospective cohort studies involving 233 patients with acute pancreatitis and splanchnic vein thrombosis. The most commonly affected vein was the splenic vein, and approximately half of the patients received anticoagulation. Pooled analyses showed no association between anticoagulation and improved clinical and radiological outcomes. The main limitation of this systematic review was the small number of available studies (36-42), and the low quality of the included studies, as no randomized or prospective studies were identified. Therefore, the potential influence of the patient's clinical context on anticoagulant decisions, known as confounding by indication, cannot be excluded. This means that no recommendation can yet be made regarding the use of anticoagulation for splanchnic vein thrombosis in acute pancreatitis. Compared to other non-pancreatitis cohorts (33), we observed a relatively low proportion of treated patients. In addition, the use of anticoagulation varied widely between different thrombus sites and between the seven studies (20-79%).

To further study the current practice of anticoagulation in this clinical context in the Netherlands, a survey and case vignette study of 93 Dutch pancreatologists is described in **Chapter 4.** The responding pancreatologists agreed on anticoagulant therapy for splanchnic vein thrombosis. Preferred indications were acute portal vein thrombosis

and thrombus progression, regardless of the presence of (suspected) infected necrosis. The majority believed that anticoagulation improved clinical outcomes. Although this is the first survey on this topic and the response rate was relatively high (67%), it is important to note that we did not use the Delphi technique to reach consensus. Therefore, it remains unknown whether these shared opinions are valid and reflect practice in other countries. It was also not possible to evaluate the treatment decision for each possible scenario. The clinical course of both splanchnic vein thrombosis and acute pancreatitis is highly variable. I believe this is exactly the reason why it is difficult to conduct high-quality, comparable studies. However, given the results of both the meta-analysis and the survey, we could hypothesize that not all splanchnic vein thromboses are treated in current practice. Perhaps this may not be necessary. In fact, the only available practice guideline on the management of splanchnic vein thrombosis in acute pancreatitis, written by the Chinese Pancreas Study Group, recommends anticoagulation specifically for thrombosis extending to the mesenteric vein and with clinical signs of bowel ischemia (43). However, the level of evidence for this recommendation is weak.

To better understand the potential role of anticoagulation, we performed a post-hoc analysis of a prospective cohort of 432 patients with necrotizing pancreatitis. As detailed in **Chapter 5**, bowel ischemia emerged as a rare but serious complication in patients with splanchnic vein thrombosis, leading to death in all cases. This indeed speaks to the severity of mesenteric vein thrombosis. We also found an association between splanchnic vein thrombosis and admission to the intensive care. The results were similar after adequate adjustment for disease severity, which was done for the first time in this study. Given this, future research should continue to focus on improving therapeutic strategies. Other relevant findings were that splanchnic vein thrombosis was detected in nearly one in four patients after a median of 4 days, while spontaneous recanalization occurred in more than half of the patients within a median of 3 weeks. Parenchymal necrosis, with left, central, or subtotal necrosis being the pattern with the highest risk, and younger age were identified as independent risk factors. These findings may have several clinical implications. First, a comprehensive evaluation of splanchnic vein thrombosis on an early computed tomography scan, often performed three to four days after onset to assess disease severity, seems to be important. Early treatment with therapeutic anticoagulation could then be considered, which has been associated with higher recanalization rates (44). Second, timely drainage of (infected) necrotic collections to prevent or treat splanchnic vein thrombosis does not seem to have a place in management. This is because both thrombus formation and recanalization occur at an early stage, in the absence of modifiable risk factors, and when collections are not yet walled off (45). Unfortunately, as with the other observational

studies, our data on anticoagulant therapy were limited by potential confounding. Therefore, this study does not add further evidence to the previous meta-analysis.

Future perspectives

Our assessment of splanchnic vein thrombosis has confirmed that the evidence for the efficacy and safety of therapeutic anticoagulation in the context of acute pancreatitis is inconclusive. Further high-quality studies are thus required. A tailored approach based on the site of thrombosis is now of particular interest and should be incorporated in these studies. Such an approach may become an alternative to the universal recommendations outlined in current thrombotic guidelines (46-49). Splanchnic vein thrombosis involves different veins originating from different organs and has different clinical consequences (50, 51). Therefore, the risk-benefit ratio may differ depending on the site of thrombosis.

A randomized controlled trial is considered the gold standard for evaluating the effectiveness of a treatment (52). However, in the case of pancreatitis-related splanchnic vein thrombosis, this may not be feasible. Especially when each thrombus site is evaluated as a separate entity. Approximately 20% of patients with acute pancreatitis progress to necrotizing pancreatitis (53). Splanchnic vein thrombosis was found in one-fifth of these patients, with involvement of the splenic vein, portal vein, and superior mesenteric vein seen in ~60%-50%-40% of cases (Chapter 5). A possible strategy to overcome the sample size problem is to extend the inclusion criteria to all provoked splanchnic vein thrombosis based on transient and local risk factors such as other abdominal infections.

Although the ultimate goal is to achieve the highest level of evidence, this does not mean that lower levels of evidence cannot be a way forward. Testing a selective anticoagulation policy in cohort studies is an interesting research method. A recent single-center retrospective study evaluated their current policy of reserving anticoagulation for all portal vein/superior mesenteric vein thrombosis and only for progressive splenic vein thrombosis, and showed improved outcomes (54). Future prospective studies are needed to provide a more detailed description of patient selection, as well as predefined selection of type and duration of anticoagulation, and follow-up. Taking into account the risk of complications, this should preferably be done with a control group not receiving anticoagulation. A multicenter study design would help to confirm the applicability to other clinical settings.

PART III – PREVENTION OF RECURRENT ACUTE PANCREATITIS

Identifying patients at risk for disease progression after a first episode of acute pancreatitis could facilitate preventive treatment strategies. Recurrent acute pancreatitis is often the first event to follow and was therefore the main focus of this part.

Chapter 6 presented the results of the longest clinical follow-up study to date of 1,184 patients with acute pancreatitis, therefore providing an accurate estimate of progression rates. Nearly one in four patients developed recurrent acute pancreatitis after their first episode. These rates were three and two times higher for alcoholic and idiopathic etiologies, respectively, than for biliary etiology. In the latter group, ERCP and cholecystectomy within 3 months after the onset of acute pancreatitis were found to be independent preventive factors. However, they were performed in less than one-third and two-third of patients, respectively. In addition to non-biliary etiologies, recurrent pancreatitis itself was an independent risk factor for chronic pancreatitis, and so was smoking. The association between acute pancreatitis and pancreatic cancer could not be properly studied because only a small subset of patients (n=14) was diagnosed with pancreatic cancer. Of these, most were diagnosed within 2 years after their presentation with idiopathic pancreatitis. This suggests an initial misdiagnosis in the first place (55). Longitudinal data on smoking and alcohol consumption were also lacking. The number of patients who completed the follow-up questionnaire on these behaviors was low. Despite these limitations, this study is clinically relevant because we have shown in which patients (and when) disease progression occurs. This can help inform patients about their expected prognosis. The risk factors identified provide guidance for improving preventive strategies such as lifestyle counseling, timely cholecystectomy, and close surveillance.

Chapter 7 described the results of the first study of the incidence of gallstones and their association with recurrent acute pancreatitis in patients with acute alcoholic pancreatitis, which was diagnosed at the discretion of the treating physician. Gallstones were present in nearly one in five patients. The recurrence rate was significantly higher in patients with gallstones who remained untreated than in those without gallstones or who underwent cholecystectomy. These results clearly indicate that a proportion of these patients do have an underlying biliary cause and that appropriate treatment can prevent recurrence of pancreatitis. As this is the first study on this topic, we were not able to make a head-to-head comparison. Other clinically relevant findings were that the evaluation of gallstones according to current guidelines and the treatment of gallstones were not performed consistently (1). So there is a lot of room for improvement. An important limitation is the lack of data on alcohol abstinence in

the recurrence-free group. There was no prospective analysis of alcohol or standard follow-up protocol. However, since more patients with gallstones were abstinent at the time of recurrence, it can be concluded that this did not affect our primary outcome. The total number of patients who achieved alcohol abstinence was, however, low. In addition, the recurrence rate after cholecystectomy was still high, which supports the need for alcohol cessation support treatment in addition to cholecystectomy.

Chapter 8 highlighted the lack of a routine management strategy in the Netherlands regarding alcohol cessation support for patients with acute alcoholic pancreatitis. This first national survey, with a response rate of 100%, showed that motivational interventions in the hospital setting and appropriate discharge planning were often not provided. As with all studies, results should be interpreted with several limitations. Local investigators who are involved in studies of the DPSG completed the survey on behalf of their gastroenterology department, which may have introduced recall bias. Also, the role of psychiatrists in supportive care was not included in the survey questions, which in retrospect was an omission. Nevertheless, standardized treatment protocols were not available in all but one of the departments surveyed. This suggests that current guidelines for problematic alcohol use are not well implemented or that clinicians are unaware of their recommendations (56-58). Either way, the findings highlight the need for improvements in the management of acute alcoholic pancreatitis.

The PANDA trial, a multicenter cluster randomized controlled trial whose protocol is presented in **Chapter 9**, was designed to compare a structured alcohol cessation support program with the current practice in patients with a first episode of acute alcoholic pancreatitis. The hypothesis is that additional efforts to reduce or stop alcohol consumption through the implementation of a structured program, including an in-hospital motivational intervention, will prevent recurrence of pancreatitis, reduce hospitalizations and costs, and improve patients' quality of life. The framework for this program was inspired by the findings in Chapter 8. The sample size calculation was based on the results presented in Chapter 6. Consistent with the findings in Chapter 7, acute alcoholic pancreatitis is diagnosed after a comprehensive diagnostic work-up, including transabdominal ultrasound to evaluate for gallstones. In the absence of evidence-based criteria for acute alcoholic pancreatitis, we use the Alcohol Use Disorder Identification Test (AUDIT), which is one of the best known and validated tools for screening for problematic alcohol use (59).

Future perspectives

In future research and current practice, it is important to prioritize optimal management in patients with acute alcoholic pancreatitis. These patients have the highest

incidence of recurrent acute pancreatitis. The management of alcoholic pancreatitis should involve a multidisciplinary team of clinicians, psychosocial care providers, and general practitioners. In addition to the PANDA trial, the Hungarian Pancreatic Study Group has initiated a randomized controlled trial (REAPPEAR) to evaluate whether a brief intervention program reduces the risk of recurrence in acute alcoholic pancreatitis (60). A trial that we can only encourage. This trial will also address smoking, an addiction that often goes hand in hand with problematic alcohol use (61). Smoking is an independent risk factor for recurrent acute pancreatitis, and even more so for chronic pancreatitis (62, 63). A combination of problematic alcohol use and smoking has been shown to have the highest cumulative risk for chronic pancreatitis (62). The results of both the PANDA and REAPPEAR trial will hopefully provide answers about the effectiveness of alcohol and smoking cessation programs and further guidance for clinical practice. In addition to my enthusiasm for these studies, I believe we should also look at the problem of alcohol from another angle. The normalization or social acceptance of alcohol use. Awareness of its harmful effects is currently lacking and should be a top priority (64). Other goals for the year 2040 are outlined in the National Prevention Agreement (65). These include measures to make alcohol less accessible and more expensive, and to regulate alcohol advertising.

With regard to idiopathic acute pancreatitis, the second etiology at risk for recurrent pancreatitis, we have recently made progress with the results of the PICUS study (66). Routine use of endoscopic ultrasound after a first episode of idiopathic acute pancreatitis resulted in lower recurrence rates by identifying the underlying etiology one-third of patients, and should be incorporated into current practice. The question now is how to improve outcomes in patients with a negative endoscopic ultrasound. The efficacy of cholecystectomy versus a conservative approach in these patients is currently being evaluated in the PICUS-2 trial. As shown, improving adherence to guidelines for the management of biliary etiology is another important issue. The evidence regarding the timing of cholecystectomy in the subset of patients with necrotizing pancreatitis requires further investigation (67). In a recent but retrospective study, the optimal timing was within 8 weeks of discharge in the absence of peripancreatic collections (68). For the remaining patients with mild biliary acute pancreatitis, there is strong evidence for the benefit of same-admission cholecystectomy (69). In my opinion, this should also be done in patients with a history of excessive alcohol consumption.

CONCLUSIONS

Clinical research on the management of acute pancreatitis was the focus of my thesis. Various treatment strategies were evaluated *'from treatment to prevention'*. Many op-

portunities to improve clinical practice and promising areas for future research were identified. The mission of the Dutch Pancreatitis Study Group to improve clinical outcomes for all patients with acute pancreatitis remains fundamental and will be continued.

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