Acute pancreatitis: from treatment to prevention

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CHAPTER 1

General introduction and thesis outline

GENERAL INTRODUCTION

In 1652, the Dutch anatomist Nicolaes Tulp initiated the exploration of acute pancreatitis by presenting its first official description as an inflammatory pancreatic disorder (1). Over 370 years later, acute pancreatitis has evolved into the most prevalent gastrointestinal disease leading to acute hospitalization (2), with its incidence continuing to rise (3). An evident illustration of this trend can be seen in the Netherlands, where hospital admissions for acute pancreatitis have witnessed a fourfold increase in the past 25 years (4, 5). This rise, potentially associated with increased lifestyle-related risk factors linked to the development of acute pancreatitis (6, 7), not only reflects its impact on patients but also the broader socioeconomic consequences. Today, in high-income countries, the most common etiologies are biliary disease and excessive alcohol consumption (8, 9). However, a variety of additional etiologies have also been acknowledged (10). Each of these etiologies involves distinct pathophysiological pathways (11, 12). Nonetheless, the ultimate common trigger is thought to be the premature activation of pancreatic enzymes, resulting in local tissue injury and inflammatory responses (13). Following the onset, patients experience severe upper abdominal pain, which leads to hospitalization where treatment is initiated (14).

The current treatment goals for acute pancreatitis are twofold (10). The first goal of treatment is to achieve symptom relief and address complications. Early treatment is restricted to supportive care and involves analgesics and fluid resuscitation, after which most patients recover within several days (15-17). In 20% of patients, the disease follows a more severe course with pancreatic and peripancreatic necrosis being the main determinant (16, 18). Secondary infection of this necrosis stands out as the most alarming complication, leading to extended hospital stays and significant morbidity and mortality (19). The second treatment goal is to prevent the recurrence of acute pancreatitis (10). Pancreatitis recurrence exposes patients to additional episodes of potential complications and increases the risk of developing chronic pancreatitis (20). A crucial aspect is the accurate detection of the underlying etiology, as each requires a different treatment approach. The guidelines recommend performing a cholecystectomy in patients with a biliary etiology and providing alcohol cessation support for patients with excessive alcohol consumption (10, 21, 22).

Since Tulp's discovery, the management of acute pancreatitis has seen significant improvements. Numerous studies, particularly focusing on infected necrotizing pancreatitis and acute biliary pancreatitis, have been conducted, wherein the Netherlands has maintained its pioneering role, mostly due to the unwavering commitment of the Dutch Pancreatitis Study Group (21, 23-26). Yet, many questions '*from treatment to prevention*' remain unanswered in current clinical practice. In this thesis, I address

several gaps in the existing literature with the aim to improve outcomes of patients with acute pancreatitis.

THESIS OUTLINE

In the first part of this thesis, I focus on the optimal timing of minimally invasive interventions for infected necrotizing pancreatitis. The second part directs the spotlight towards a less frequently discussed complication known as splanchnic vein thrombosis, and explores the evidence supporting the use of anticoagulant therapy as part of its treatment. In the third part, I concentrate on strategies for preventing recurrence after the initial episode of acute pancreatitis.

PART I – TREATMENT OF INFECTED NECROTIZING PANCREATITIS

Infected necrosis develops in approximately one-third of patients with necrotizing pancreatitis (16). This condition is believed to result from the translocation of intestinal bacteria across the gut mucosa (27). While there have been attempts to prevent secondary infection using prophylactic systemic antibiotics or enteral probiotics, no beneficial effect has been proven, making such interventions not recommended (28, 29). However, if the diagnosis is confirmed through imaging or microbiological culture, or if there is suspicion based on clinical deterioration, intravenous broad-spectrum antibiotics should be initiated (10, 30), with a pancreatic intervention often taking place thereafter (16, 31, 32). Until the 2010 publication of the PANTER trial, open surgical necrosectomy was the standard initial intervention (23). This trial demonstrated the superiority of a minimally invasive surgical 'step-up' approach – involving percutaneous catheter drainage and, when necessary, laparoscopic necrosectomy – over the traditional open method. Following advancements in endoscopic techniques, the 2018 TENSION trial compared the endoscopic step-up approach, comprising endoscopic transluminal drainage followed by endoscopic necrosectomy, to the surgical step-up approach (24). The results favored the endoscopic group, showing shorter hospital stays and fewer pancreaticocutaneous fistulas. Consequently, the endoscopic step-up approach is now considered the best practice for patients with endoscopically accessible infected necrotic collections (33). Another important topic in the treatment of infected necrotizing pancreatitis is determining the best timing for initiating catheter drainage. This was explored in the recent POINTER trial conducted by the Dutch Pancreatitis Study Group (26). In this multicenter trial, 104 patients with infected necrotizing pancreatitis were randomly assigned to immediate drainage

following diagnosis or postponed drainage until the stage of walled-off necrosis. The results showed no differences in mortality and complication rates. However, among patients treated with the postponed drainage approach, fewer interventions were needed, and more than a third did not undergo any drainage procedure throughout a 6-month follow-up. Yet, the long-term advantages of this approach remain unknown. It is hypothesized that infected necrotic collections, when treated conservatively with only antibiotics, could lead to persistent or long-term complications that require interventions during extended follow-ups. Therefore, in **Chapter 2**, the POINTER trial's long-term follow-up is described. This study compares the long-term clinical outcomes of patients with infected necrotizing pancreatitis who underwent either an immediate or postponed drainage approach.

PART II – SPLANCHNIC VEIN THROMBOSIS IN ACUTE PANCREATITIS

The splanchnic venous system drains the gastrointestinal organs and consists of the portal vein, splenic vein, and superior mesenteric vein (34). Due to their proximity to the pancreas, these veins are susceptible to complications during episodes of acute pancreatitis, especially in cases of necrotizing pancreatitis (35). Splanchnic vein thrombosis is a vascular complication found in 2% to 51% of acute pancreatitis patients, primarily influenced by the severity of the disease (36-38). This thrombosis can manifest as an intraluminal filling defect on contrast-enhanced computed tomography (39). The development of splanchnic vein thrombosis in acute (necrotizing) pancreatitis is attributed to several mechanisms (34, 40), all of which align with the principles of Virchow's Triad (41). Firstly, pancreatic edema and inflammation may result in venous stasis. Additionally, the presence of pancreatic or peripancreatic collections can further contribute to this stasis. Secondly, acute pancreatitis can initiate a systemic inflammatory response, the extent of which typically parallels disease severity, leading to hypercoagulability. Lastly, both necrotic tissue and the release of activated pancreatic enzymes may directly damage vascular endothelial cells.

A primary challenge with this vascular complication is the lack of standardized treatment guidelines tailored for acute pancreatitis (10). Available guidelines advocating therapeutic anticoagulants use lean heavily on studies focused on patients with persistent thrombotic risk (42-45). This contrasts with the transient inflammatory nature of acute pancreatitis, raising questions about the efficacy of anticoagulant therapy in these patients. In **Chapter 3**, a systematic review and meta-analysis of all available evidence to assess whether therapeutic anticoagulants improve clinical outcomes in patients with acute pancreatitis and splanchnic vein thrombosis is presented.

Without evidence-based recommendations, clinicians often rely on their own judgement for treatment decisions. To date, the collective opinion of pancreatologists on therapeutic anticoagulation remains unknown. One notable concern in clinical settings is the risk of bleeding. Necrotizing pancreatitis can directly erode blood vessels, leading to pseudoaneurysm formation (46). Furthermore, complications such as infected necrosis frequently demand invasive interventions, further increasing the risk of bleeding (47). **Chapter 4** describes a survey and case-vignette study among Dutch pancreatologists to evaluate their current perspectives on using therapeutic anticoagulants for splanchnic vein thrombosis in acute pancreatitis.

Similar to anticoagulant therapy, there is limited knowledge about the natural progression of splanchnic vein thrombosis in acute pancreatitis and its associated complications. While some believe that its course is primarily driven by the pancreatitis itself, this condition can lead to severe complications, such as hypertensive bleeding and small bowel ischemia (48, 49). Gaining insight into this is vital, as it might influence treatment decisions. Most prior studies were of limited scale and lacked a comparative group without thrombosis (46, 50-52). **Chapter 5** summarizes the full clinical impact of splanchnic vein thrombosis, utilizing a large, observational, multicenter cohort study of patients with necrotizing pancreatitis.

PART III – PREVENTION OF RECURRENT ACUTE PANCREATITIS

Embracing the age-old saying that 'Prevention is better than cure,' the focus shifted from treatments to preventive strategies for disease progression. Over the years, the paradigm that acute, recurrent, and chronic pancreatitis are separate disease entities has evolved into the concept of a disease continuum. Some patients with acute pancreatitis will develop chronic pancreatitis, often encountering recurrent episodes of acute pancreatitis in between (53-55). Moreover, patients with chronic pancreatitis may even progress to pancreatic cancer (56, 57). Whether acute pancreatitis is associated with pancreatic cancer is a matter of continued debate (58). **Chapter 6** begins by examining statistics and risk factors that influence disease progression in an observational long-term follow-up cohort study.

As previously mentioned, guided preventive treatments depend on the accurate diagnosis of the underlying etiology (10). Imaging techniques such as (endoscopic) ultrasound and magnetic resonance cholangiopancreatography are currently used to assess the biliary system for gallstones (59, 60). In daily practice, gallstones identified through these imaging modalities might be overlooked or remain untreated in patients

with acute pancreatitis who consume excessive amounts of alcohol. This lack of action potentially increases the risk of pancreatitis recurrence and other biliary complications (21). In **Chapter 7**, an observational study from a prospective multicenter cohort is summarized. This study assesses the incidence and clinical relevance of gallstones in patients presumed to have acute alcoholic pancreatitis.

After diagnosing an alcoholic etiology, it is important to address alcohol consumption, the main preventable risk factor for recurrent episodes (53, 61). While prior research, varying in follow-up durations, reported recurrence rates between 24% and 46% (53, 62-64), these rates dropped close to zero with the achievement of alcohol cessation (62, 64). This underscores the urgency of attempts to reduce alcohol consumption. Although guidelines emphasize dedicated follow-up visits, they fall short of proposing a concrete treatment plan. **Chapter 8** introduces a nationwide survey aimed to assess current practices related to alcohol cessation support for patients with acute alcoholic pancreatitis, spotlighting potential areas for improvement.

A 2009 Finnish trial demonstrated encouraging outcomes from repeated motivational interventions compared to a single session for patients with acute alcoholic pancreatitis (22). However, the true effectiveness of this intervention may be overestimated, considering that participants in a traditional randomized trial were likely those potentially motivated to quit or reduce alcohol. Therefore, the multicenter cluster randomized PANDA trial is described in **Chapter 9**. This trial investigates whether implementation of a structured alcohol cessation support program, as compared to current practice, reduces the recurrence of pancreatitis in patients after their first episode of acute alcoholic pancreatitis.

REFERENCES

1. Tulp N. Observationum medicarum Editio nova et actua [Medical Observations. New and Enlarged Edition]. Vol Book 4. 2nd ed. Amsterdam, the Netherlands; 1652.
2. Internet, cited October 22, 2022 Health & Social Care Information Centre. Hospital episode statistics, admitted patient care - England, 2014-15. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient.
3. Iannuzzi JP, King JA, Leong JH, Quan J, Windsor JW, Tanyingoh D, Coward S, Forbes N, Heitman SJ, Shaheen AA, Swain M, Buie M, Underwood FE, Kaplan GG. Global Incidence of Acute Pancreatitis Is Increasing Over Time: A Systematic Review and Meta-Analysis. Gastroenterology. 2022 Jan;162(1):122-134. doi: 10.1053/j.gastro.2021.09.043.
4. Spanier BW, Dijkgraaf MG, Bruno MJ. Trends and forecasts of hospital admissions for acute and chronic pancreatitis in the Netherlands. Eur J Gastroenterol Hepatol. 2008 Jul;20(7):653-8. doi: 10.1097/MEG.0b013e3282f52f83.
5. Spanier BWM, Bruno M, Dijkgraaf M. An update on hospital admissions for acute pancreatitis in the Netherlands (2013-2019). Eur J Gastroenterol Hepatol. 2022 Jun 1;34(6):726-727. doi: 10.1097/MEG.0000000000002360.
6. Alsamarrai A, Das SL, Windsor JA, Petrov MS. Factors that affect risk for pancreatic disease in the general population: a systematic review and meta-analysis of prospective cohort studies. Clin Gastroenterol Hepatol. 2014 Oct;12(10):1635-44.e5; quiz e103. doi: 10.1016/j.cgh.2014.01.038.
7. Sadr-Azodi O, Andrén-Sandberg Å, Orsini N, Wolk A. Cigarette smoking, smoking cessation and acute pancreatitis: a prospective population-based study. Gut. 2012 Feb;61(2):262-7. doi: 10.1136/gutjnl-2011-300566.
8. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017 Mar-Apr;17(2):155-165. doi: 10.1016/j.pan.2017.01.005.
9. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas. 2006 Nov;33(4):323-30. doi: 10.1097/01.mpa.0000236733.31617.52.
10. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013 Jul-Aug;13(4 Suppl 2):e1-15. doi: 10.1016/j.pan.2013.07.063.
11. Sah RP, Dawra RK, Saluja AK. New insights into the pathogenesis of pancreatitis. Curr Opin Gastroenterol. 2013 Sep;29(5):523-30. doi: 10.1097/MOG.0b013e328363e399.
12. Weiss FU, Laemmerhirt F, Lerch MM. Etiology and Risk Factors of Acute and Chronic Pancreatitis. Visc Med. 2019 Apr;35(2):73-81. doi: 10.1159/000499138.
13. Mayerle J, Weiss FU, Halangk W, Lerch MM. Molecular, biochemical, and metabolic abnormalities of acute pancreatitis. The Pancreas: an integrated textbook of basic science, medicine, and surgery. Third edition. 2018. .
14. Boxhoorn L, Voermans RP, Bouwense SA, Bruno MJ, Verdonk RC, Boermeester MA, van Santvoort HC, Besselink MG. Acute pancreatitis. Lancet. 2020 Sep 5;396(10252):726-734. doi: 10.1016/S0140-6736(20)31310-6.
15. Buxbaum JL, Quezada M, Da B, Jani N, Lane C, Mwengela D, Kelly T, Jhun P, Dhanireddy K, Laine L. Early Aggressive Hydration Hastens Clinical Improvement in Mild Acute Pancreatitis. Am J Gastroenterol. 2017 May;112(5):797-803. doi: 10.1038/ajg.2017.40.
16. van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, Boermeester MA, van Goor H, Dejong CH, van Eijck CH, van Ramshorst B, Schaapherder AF, van der Harst E, Hofker S, Nieuwenhuijs VB, Brink MA, Kruyt PM, Manusama ER, van der Schelling

GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, Cuesta MA, Wahab PJ, Gooszen HG; Dutch Pancreatitis Study Group. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology. 2011 Oct;141(4):1254-63. doi: 10.1053/j.gastro.2011.06.073.

17. Bakker OJ, van Santvoort H, Besselink MG, Boermeester MA, van Eijck C, Dejong K, van Goor H, Hofker S, Ahmed Ali U, Gooszen HG, Bollen TL; Dutch Pancreatitis Study Group. Extrapancreatic necrosis without pancreatic parenchymal necrosis: a separate entity in necrotising pancreatitis? Gut. 2013 Oct;62(10):1475-80. doi: 10.1136/gutjnl-2012-302870.
18. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013 Jan;62(1):102-11. doi: 10.1136/gutjnl-2012-302779.
19. Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, van Santvoort HC, Bruno MJ; Dutch Pancreatitis Study Group. Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis. Gut. 2019 Jun;68(6):1044-1051. doi: 10.1136/gutjnl-2017-314657.
20. Nøjgaard C, Becker U, Matzen P, Andersen JR, Holst C, Bendtsen F. Progression from acute to chronic pancreatitis: prognostic factors, mortality, and natural course. Pancreas. 2011 Nov;40(8):1195-200. doi: 10.1097/MPA.0b013e318221f569.
21. da Costa DW, Bouwense SA, Schepers NJ, Besselink MG, van Santvoort HC, van Brunschot S, Bakker OJ, Bollen TL, Dejong CH, van Goor H, Boermeester MA, Bruno MJ, van Eijck CH, Timmer R, Weusten BL, Consten EC, Brink MA, Spanier BWM, Bilgen EJS, Nieuwenhuijs VB, Hofker HS, Rosman C, Voorburg AM, Bosscha K, van Duijvendijk P, Gerritsen JJ, Heisterkamp J, de Hingh IH, Witteman BJ, Kruyt PM, Scheepers JJ, Molenaar IQ, Schaapherder AF, Manusama ER, van der Waaij LA, van Unen J, Dijkgraaf MG, van Ramshorst B, Gooszen HG, Boerma D; Dutch Pancreatitis Study Group. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. Lancet. 2015 Sep 26;386(10000):1261-1268. doi: 10.1016/S0140-6736(15)00274-3.
22. Nordback I, Pelli H, Lappalainen-Lehto R, Järvinen S, Räty S, Sand J. The recurrence of acute alcohol-associated pancreatitis can be reduced: a randomized controlled trial. Gastroenterology. 2009 Mar;136(3):848-55. doi: 10.1053/j.gastro.2008.11.044.
23. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, van Goor H, Schaapherder AF, van Eijck CH, Bollen TL, van Ramshorst B, Nieuwenhuijs VB, Timmer R, Laméris JS, Kruyt PM, Manusama ER, van der Harst E, van der Schelling GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, van Leeuwen MS, Buskens E, Gooszen HG; Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010 Apr 22;362(16):1491-502. doi: 10.1056/NEJMoa0908821.
24. van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, Bollen TL, Bosscha K, Bouwense SA, Bruno MJ, Cappendijk VC, Consten EC, Dejong CH, van Eijck CH, Erkelens WG, van Goor H, van Grevenstein WMU, Haveman JW, Hofker SH, Jansen JM, Laméris JS, van Lienden KP, Meijssen MA, Mulder CJ, Nieuwenhuijs VB, Poley JW, Quispel R, de Ridder RJ, Römkens TE, Scheepers JJ, Schepers NJ, Schwartz MP, Seerden T, Spanier BWM, Straathof JWA, Strijker M, Timmer R, Venneman NG, Vleggaar FP, Voermans RP, Witteman BJ, Gooszen HG, Dijkgraaf MG, Fockens P; Dutch Pancreatitis Study Group. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: a multicentre randomised trial. Lancet. 2018 Jan 6;391(10115):51-58. doi: 10.1016/S0140-6736(17)32404-2.

25. Schepers NJ, Hallensleben NDL, Besselink MG, Anten MGF, Bollen TL, da Costa DW, van Delft F, van Dijk SM, van Dullemen HM, Dijkgraaf MGW, van Eijck CHJ, Erkelens GW, Erler NS, Fockens P, van Geenen EJM, van Grinsven J, Hollemans RA, van Hooft JE, van der Hulst RWM, Jansen JM, Kubben FJGM, Kuiken SD, Laheij RJF, Quispel R, de Ridder RJJ, Rijk MCM, Römkens TEH, Ruigrok CHM, Schoon EJ, Schwartz MP, Smeets XJNM, Spanier BWM, Tan ACITL, Thijs WJ, Timmer R, Venneman NG, Verdonk RC, Vleggaar FP, van de Vrie W, Witteman BJ, van Santvoort HC, Bakker OJ, Bruno MJ; Dutch Pancreatitis Study Group. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): a multicentre randomised controlled trial. Lancet. 2020 Jul 18;396(10245):167-176. doi: 10.1016/S0140-6736(20)30539-0.
26. Boxhoorn L, van Dijk SM, van Grinsven J, Verdonk RC, Boermeester MA, Bollen TL, Bouwense SAW, Bruno MJ, Cappendijk VC, Dejong CHC, van Duijvendijk P, van Eijck CHJ, Fockens P, Francken MFG, van Goor H, Hadithi M, Hallensleben NDL, Haveman JW, Jacobs MAJM, Jansen JM, Kop MPM, van Lienden KP, Manusama ER, Mieog JSD, Molenaar IQ, Nieuwenhuijs VB, Poen AC, Poley JW, van de Poll M, Quispel R, Römkens TEH, Schwartz MP, Seerden TC, Stommel MWJ, Straathof JWA, Timmerhuis HC, Venneman NG, Voermans RP, van de Vrie W, Witteman BJ, Dijkgraaf MGW, van Santvoort HC, Besselink MG; Dutch Pancreatitis Study Group. Immediate versus Postponed Intervention for Infected Necrotizing Pancreatitis. N Engl J Med. 2021 Oct 7;385(15):1372-1381. doi: 10.1056/NEJMoa2100826.
27. Mowbray NG, Ben-Ismaeil B, Hammoda M, Shingler G, Al-Sarireh B. The microbiology of infected pancreatic necrosis. Hepatobiliary Pancreat Dis Int. 2018 Oct;17(5):456-460. doi: 10.1016/j.hbpd.2018.08.007.
28. Lim CL, Lee W, Liew YX, Tang SS, Chlebicki MP, Kwa AL. Role of antibiotic prophylaxis in necrotizing pancreatitis: a meta-analysis. J Gastrointest Surg. 2015 Mar;19(3):480-91. doi: 10.1007/s11605-014-2662-6.
29. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Rosman C, Ploeg RJ, Brink MA, Schaapherder AF, Dejong CH, Wahab PJ, van Laarhoven CJ, van der Harst E, van Eijck CH, Cuesta MA, Akkermans LM, Gooszen HG; Dutch Acute Pancreatitis Study Group. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008 Feb 23;371(9613):651-659. doi: 10.1016/S0140-6736(08)60207-X.
30. Baron TH, DiMaio CJ, Wang AY, Morgan KA. American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis. Gastroenterology. 2020 Jan;158(1):67-75.e1. doi: 10.1053/j.gastro.2019.07.064.
31. Adler DG, Chari ST, Dahl TJ, Farnell MB, Pearson RK. Conservative management of infected necrosis complicating severe acute pancreatitis. Am J Gastroenterol. 2003 Jan;98(1):98-103. doi: 10.1111/j.1572-0241.2003.07162.x.
32. Runzi M, Niebel W, Goebell H, Gerken G, Layer P. Severe acute pancreatitis: nonsurgical treatment of infected necroses. Pancreas. 2005 Apr;30(3):195-9. doi: 10.1097/01.mpa.0000153613.
33. Arvanitakis M, Dumonceau JM, Albert J, Badaoui A, Bali MA, Barthet M, Besselink M, Deviere J, Oliveira Ferreira A, Gyökeres T, Hritz I, Hucl T, Milashka M, Papanikolaou IS, Poley JW, Seewald S, Vanbiervliet G, van Lienden K, van Santvoort H, Voermans R, Delhaye M, van Hooft J. Endoscopic management of acute necrotizing pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) evidence-based multidisciplinary guidelines. Endoscopy. 2018 May;50(5):524-546. doi: 10.1055/a-0588-5365.

34. Mendelson RM, Anderson J, Marshall M, Ramsay D. Vascular complications of pancreatitis. ANZ J Surg. 2005 Dec;75(12):1073-9. doi: 10.1111/j.1445-2197.2005.03607.x.
35. Nadkarni NA, Khanna S, Vege SS. Splanchnic venous thrombosis and pancreatitis. Pancreas. 2013 Aug;42(6):924-31. doi: 10.1097/MPA.0b013e318287cd3d.
36. Anis FS, Adiamah A, Lobo DN, Sanyal S. Incidence and treatment of splanchnic vein thrombosis in patients with acute pancreatitis: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2022 Mar;37(3):446-454. doi: 10.1111/jgh.15711.
37. Butler JR, Eckert GJ, Zyromski NJ, Leonardi MJ, Lillemoe KD, Howard TJ. Natural history of pancreatitis-induced splenic vein thrombosis: a systematic review and meta-analysis of its incidence and rate of gastrointestinal bleeding. HPB (Oxford). 2011 Dec;13(12):839-45. doi: 10.1111/j.1477-2574.2011.00375.x.
38. Xu W, Qi X, Chen J, Su C, Guo X. Prevalence of Splanchnic Vein Thrombosis in Pancreatitis: A Systematic Review and Meta-Analysis of Observational Studies. Gastroenterol Res Pract. 2015;2015:245460. doi: 10.1155/2015/245460.
39. Sturm L, Bettinger D, Klinger C, Krauss T, Engel H, Huber JP, Schmidt A, Caca K, Thimme R, Schultheiss M. Validation of color Doppler ultrasound and computed tomography in the radiologic assessment of non-malignant acute splanchnic vein thrombosis. PLoS One. 2021 Dec 20;16(12):e0261499. doi: 10.1371/journal.pone.0261499.
40. Kalas MA, Leon M, Chavez LO, Canalizo E, Surani S. Vascular complications of pancreatitis. World J Clin Cases. 2022 Aug 6;10(22):7665-7673. doi: 10.12998/wjcc.v10.i22.7665.
41. Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol. 2008 Oct;143(2):180-90. doi: 10.1111/j.1365-2141.2008.07323.x.
42. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016 Feb;149(2):315-352. doi: 10.1016/j.chest.2015.11.026.
43. de Franchis R; Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. 2015 Sep;63(3):743-52. doi: 10.1016/j.jhep.2015.05.022.
44. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Vascular diseases of the liver. J Hepatol. 2016 Jan;64(1):179-202. doi: 10.1016/j.jhep.2015.07.040.
45. DeLeve LD, Valla DC, Garcia-Tsao G; American Association for the Study Liver Diseases. Vascular disorders of the liver. Hepatology. 2009 May;49(5):1729-64. doi: 10.1002/hep.22772.
46. Maatman TK, Heimberger MA, Lewellen KA, Roch AM, Colgate CL, House MG, Nakeeb A, Ceppa EP, Schmidt CM, Zyromski NJ. Visceral artery pseudoaneurysm in necrotizing pancreatitis: incidence and outcomes. Can J Surg. 2020 May 21;63(3):E272-E277. doi: 10.1503/cjs.009519.
47. Shen X, Sun J, Zhang J, Ke L, Tong Z, Li G, Jiang W, Li W, Li J. Risk Factors and Outcome for Massive Intra-Abdominal Bleeding Among Patients With Infected Necrotizing Pancreatitis. Medicine (Baltimore). 2015 Jul;94(28):e1172. doi: 10.1097/MD.0000000000001172.
48. Spaander MC, Hoekstra J, Hansen BE, Van Buuren HR, Leebeek FW, Janssen HL. Anticoagulant therapy in patients with non-cirrhotic portal vein thrombosis: effect on new thrombotic events and gastrointestinal bleeding. J Thromb Haemost. 2013 Mar;11(3):452-9. doi: 10.1111/jth.12121.
49. Valeriani E, Riva N, Di Nisio M, Ageno W. Splanchnic Vein Thrombosis: Current Perspectives. Vasc Health Risk Manag. 2019 Oct 22;15:449-461. doi: 10.2147/VHRM.S197732.

50. Easler J, Muddana V, Furlan A, Dasyam A, Vipperla K, Slivka A, Whitcomb DC, Papachristou GI, Yadav D. Portosplenomesenteric venous thrombosis in patients with acute pancreatitis is associated with pancreatic necrosis and usually has a benign course. Clin Gastroenterol Hepatol. 2014 May;12(5):854-62. doi: 10.1016/j.cgh.2013.09.068.
51. Gonzelez HJ, Sahay SJ, Samadi B, Davidson BR, Rahman SH. Splanchnic vein thrombosis in severe acute pancreatitis: a 2-year, single-institution experience. HPB (Oxford). 2011 Dec;13(12):860-4. doi: 10.1111/j.1477-2574.2011.00392.x.
52. Pagliari D, Cianci R, Brizi MG, Mancarella FA, Musso M, Cintoni M, Franza L, Flore RA, Gasbarrini A, Tondi P. Anticoagulant therapy in the treatment of splanchnic vein thrombosis associated to acute pancreatitis: a 3-year single-centre experience. Intern Emerg Med. 2020 Sep;15(6):1021-1029. doi: 10.1007/s11739-019-02271-5.
53. Ahmed Ali U, Issa Y, Hagenaars JC, Bakker OJ, van Goor H, Nieuwenhuijs VB, Bollen TL, van Ramshorst B, Witteman BJ, Brink MA, Schaapherder AF, Dejong CH, Spanier BW, Heisterkamp J, van der Harst E, van Eijck CH, Besselink MG, Gooszen HG, van Santvoort HC, Boermeester MA; Dutch Pancreatitis Study Group. Risk of Recurrent Pancreatitis and Progression to Chronic Pancreatitis After a First Episode of Acute Pancreatitis. Clin Gastroenterol Hepatol. 2016 May;14(5):738-46. doi: 10.1016/j.cgh.2015.12.040.
54. Lankisch PG, Breuer N, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P. Natural history of acute pancreatitis: a long-term population-based study. Am J Gastroenterol. 2009 Nov;104(11):2797-805; quiz 2806. doi: 10.1038/ajg.2009.405.
55. Yadav D, O'Connell M, Papachristou GI. Natural history following the first attack of acute pancreatitis. Am J Gastroenterol. 2012 Jul;107(7):1096-103. doi: 10.1038/ajg.2012.126.
56. Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic Pancreatitis and Pancreatic Cancer Risk: A Systematic Review and Meta-analysis. Am J Gastroenterol. 2017 Sep;112(9):1366-1372. doi: 10.1038/ajg.2017.218.
57. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, Dimagno EP, Andrén-Sandberg A, Domellöf L. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med. 1993 May 20;328(20):1433-7. doi: 10.1056/NEJM199305203282001.
58. Umans DS, Hoogenboom SA, Sissingh NJ, Lekkerkerker SJ, Verdonk RC, van Hooft JE. Pancreatitis and pancreatic cancer: A case of the chicken or the egg. World J Gastroenterol. 2021 Jun 21;27(23):3148-3157. doi: 10.3748/wjg.v27.i23.3148.
59. Wan J, Ouyang Y, Yu C, Yang X, Xia L, Lu N. Comparison of EUS with MRCP in idiopathic acute pancreatitis: a systematic review and meta-analysis. Gastrointest Endosc. 2018 May;87(5):1180-1188.e9. doi: 10.1016/j.gie.2017.11.028.
60. Umans DS, Rangkuti CK, Sperna Weiland CJ, Timmerhuis HC, Bouwense SAW, Fockens P, Besselink MG, Verdonk RC, van Hooft JE; Dutch Pancreatitis Study Group. Endoscopic ultrasonography can detect a cause in the majority of patients with idiopathic acute pancreatitis: a systematic review and meta-analysis. Endoscopy. 2020 Nov;52(11):955-964. doi: 10.1055/a-1183-3370.
61. Bertilsson S, Swärd P, Kalaitzakis E. Factors That Affect Disease Progression After First Attack of Acute Pancreatitis. Clin Gastroenterol Hepatol. 2015 Sep;13(9):1662-9.e3. doi: 10.1016/j.cgh.2015.04.012.
62. Pelli H, Lappalainen-Lehto R, Piironen A, Sand J, Nordback I. Risk factors for recurrent acute alcohol-associated pancreatitis: a prospective analysis. Scand J Gastroenterol. 2008;43(5):614-21. doi: 10.1080/00365520701843027.

63. Pelli H, Sand J, Laippala P, Nordback I. Long-term follow-up after the first episode of acute alcoholic pancreatitis: time course and risk factors for recurrence. Scand J Gastroenterol. 2000 May;35(5):552-5. doi: 10.1080/003655200750023840.

64. Nikkola J, Räty S, Laukkarinen J, Seppänen H, Lappalainen-Lehto R, Järvinen S, Nordback I, Sand J. Abstinence after first acute alcohol-associated pancreatitis protects against recurrent pancreatitis and minimizes the risk of pancreatic dysfunction. Alcohol Alcohol. 2013 Jul-Aug;48(4):483-6. doi: 10.1093/alcalc/agt019.