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Multidisciplinary management of severe acute pancreatitis

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Publication date
2022

[Link to publication](#)

Citation for published version (APA):

Boxhoorn, L. (2022). *Multidisciplinary management of severe acute pancreatitis*. [Thesis, fully internal, Universiteit van Amsterdam].

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Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Acute pancreatitis is an inflammatory disease of the pancreas, most commonly caused by gallstones or alcohol ingestion, and one of the most prevalent gastrointestinal diseases leading to hospital admission. In the past 5 years, approximately 7000 patients with acute pancreatitis were admitted in the Netherlands.¹ Patients with mild acute pancreatitis often recover quickly, but 20% of patients develop a moderate or severe form of acute pancreatitis, with organ failure or necrosis of the pancreatic and peripancreatic tissue.^{2,3} Patients can become critically ill when pancreatic or peripancreatic necrotic tissue becomes infected.³ Treatment of severe acute pancreatitis therefore still presents significant challenges to the multidisciplinary team of gastroenterologists, surgeons, interventional radiologists and intensive care specialists.

While the management of severe acute pancreatitis has improved considerably over the years, there continue to be many unanswered questions in daily clinical practice. To better understand the current treatment gaps, it is important to know how treatment has changed since the earliest reported cases of acute pancreatitis. This thesis therefore starts with a timeline, highlighting the major discoveries and developments in the treatment of severe acute pancreatitis according to literature.

History of acute pancreatitis

The first description of acute pancreatitis in literature is probably dated 323 before Christ. According to several historical sources, no one less than Alexander the Great suffered from acute pancreatitis.⁴ Shortly after Alexander the Great hosted an extravagant celebration dinner after returning from his latest victory in the East, he rapidly deteriorated and suffered from severe abdominal pain and vomiting. Alexander the Great eventually died of sepsis, only a few days before his 33rd birthday. Although for many years, it was a widely accepted theory that Alexander the Great was poisoned, the aforementioned symptoms might suggest an attack of acute pancreatitis.

The first official description of acute pancreatitis was, however, published a considerable time later. The well-known Dutch doctor and anatomist Nicolaes Tulp (1593-1674) described the anatomical findings of acute pancreatitis in 1652.⁵ In 1889, Reginald Fitz systematically presented the clinical symptoms of 53 patients with acute pancreatitis.⁶ He distinguished three 'types' of disease: hemorrhagic, suppurative and gangrenous acute pancreatitis.⁶ With regards to treatment, the renowned surgeon Nicholas Senn first presented his surgical experience on the pancreas in 1886.⁷ Senn described several surgical procedures in his article, including partial and total pancreatectomy. He advocated a

conservative approach, because surgical intervention could lead to damage or necrosis of the duodenum.⁷ In the late 19th and at the beginning of the 20th century, the conservative standpoint remained, although it was often debated whether surgery would improve clinical outcome. The surgeons therefore returned to the scene in the 1980s, with open necrosectomy procedures for patients developing necrotizing pancreatitis.⁸⁻¹⁰ Based on research in the subsequent years, two types of pancreatic necrosis were distinguished: infected and sterile necrosis.¹¹⁻¹³ With this distinction, it became generally accepted to stay conservative in patients with sterile necrosis and perform open surgical necrosectomy in patients with infected necrosis. However, the practice of open necrosectomy was formally challenged by the results of the Dutch multicenter PANTER trial in 2010, which demonstrated the superiority of a minimally invasive 'step-up approach' over open necrosectomy.¹⁴ As a result, the therapeutic approach of patients with infected necrosis changed from open procedures to minimally invasive approaches – which led to a substantial reduction in morbidity and mortality.¹⁵

During that period, gastroenterologists became more frequently involved, mainly due to the development of endoscopic techniques. The first successful endoscopic transluminal drainage procedure was described in 1996, and eventually endoscopic ultrasound was integrated.¹⁶ The findings from two Dutch trials suggested that endoscopic treatment would be a promising alternative to surgery. The PENGUIN trial, that was published in 2012, compared endoscopic transluminal necrosectomy to surgical necrosectomy in 22 patients with infected necrosis.¹⁷ The findings of this trial demonstrated that endoscopic transluminal necrosectomy significantly reduced the inflammatory response, complications and death. Subsequently, the TENSION trial compared the endoscopic step-up approach to the surgical step-up approach in 2018.¹⁸ The results demonstrated no differences in mortality or major complications, but hospital stay in the endoscopy group was shorter and patients also developed fewer pancreaticocutaneous fistulas. Shortly after, the American MISER trial compared the endoscopic step-up approach to minimally invasive surgical procedures.¹⁹ The trial results also demonstrated no differences in mortality, but the endoscopic step-up approach did lead to less complications, in particular less enteral and pancreaticocutaneous fistulas. The same authors were also the first to look into the use of lumen-apposing metal stents (LAMS) instead of the conventional double-pigtail plastic stents for endoscopic transluminal drainage. The wider lumen diameter of the LAMS, in theory, improves drainage and gives direct endoscopic access to remove large pieces of necrosis. In 2018, they found no difference in the total number of interventions, hospital stay or overall treatment costs in a randomized trial.²⁰ LAMS were, however, associated with a higher rate of complications, and are currently still topic of ongoing debate.²¹

This historical context demonstrates that the treatment of severe acute pancreatitis has evolved rapidly in the past decade. Nevertheless, many treatment challenges still remain. In my thesis, I will focus on several important knowledge gaps in literature, which I will further address in the thesis outline below.

THESIS OUTLINE

Part I - Evidenced-based overview at the start of this thesis

The first part of my thesis, **Chapter 2**, begins with an evidenced-based overview on the diagnosis, classification and treatment of patients with acute pancreatitis based on the available literature at the start of my PhD trajectory.

Part II - Timing of step-up approach

The second part of my thesis addresses the best timing of minimally invasive interventions for patients with infected necrosis. As mentioned, the minimally invasive 'step-up approach' is currently considered best practice for patients with infected necrotizing pancreatitis.^{22,23} The first step of this strategy is catheter drainage, which can either performed image-guided percutaneously or endoscopically.^{22,23} As a common practice, this drainage procedure is nearly always delayed until necrosis becomes encapsulated, also known as 'walled-off necrosis', along with administering antibiotics.²²⁻²⁴ This practice originates from the time of open necrosectomy, when a postponed procedure was associated with fewer complications.²⁵⁻²⁸ Additionally, some patients recover during this delay with supportive care and antibiotic treatment.²⁸⁻³⁰ This strategy is, nonetheless, often questioned by experts in the field.³¹ Theoretically, walled-off necrosis might not be required for the current minimally invasive interventions.³²⁻³⁴ A long course of antibiotics has some disadvantages, such as fungal infections and antibiotic resistance.²⁶ But most importantly, immediate drainage after diagnosing infected necrosis might benefit the patient's clinical outcome. In **Chapter 3** of this thesis, the timing of catheter drainage is studied in the randomized controlled multicenter POINTER trial. This trial addresses the question whether early catheter drainage, as soon as infected necrosis is diagnosed, is superior to postponed catheter drainage in patients with infected necrotizing pancreatitis.

Part III - The endoscopic step-up approach

The endoscopic step-up approach is favored over a surgical step-up approach in eligible patients. Nevertheless, there are several questions related to this approach, which will be addressed in the third part of this thesis.

LAMS are a relatively new device for endoscopic transluminal drainage, potentially replacing double-pigtail plastic stents (DPS). Supposedly, LAMS contribute to easier and better endoscopic transluminal drainage of infected necrosis when compared to DPS. Nevertheless, the use of LAMS is associated with severe complications.²¹ Thus, the

discussion on the most appropriate device for endoscopic transluminal drainage remains unsettled. Therefore, the prospective multicenter AXIOMA study is described in **Chapter 4**. This study compares the clinical outcome of patients with infected necrosis who were drained endoscopically with LAMS to those of patients drained with DPS.

The subsequent chapter determines to evaluate the long-term outcomes of patients with infected necrotizing pancreatitis. The short-term outcomes of endoscopic step-up approach might be favourable over the surgical approach, but the advantages for the longer term are unknown. The higher number of pancreaticocutaneous fistulas associated with the surgical step-up approach might result in additional interventions and an impaired quality of life. Therefore, in **Chapter 5**, the ExTENSION long-term follow-up study is described. This study evaluates the long-term clinical outcomes following an endoscopic or surgical step-up approach for infected necrotising pancreatitis.

The final chapter of the third part of this thesis is related to the treatment of patients with symptomatic sterile necrosis. Pancreatic and peripancreatic necrosis often remains sterile and will resolve spontaneously over time; those patients are usually treated without an intervention.³⁵ But when necrotic collections do not resolve spontaneously, they can cause debilitating symptoms, such as abdominal pain, gastric outlet obstruction, jaundice or failure to thrive. If such symptoms persist, drainage can be considered in line with the current guidelines.²² But drainage might not always be the right solution, because of the risk of introducing micro-organisms in a sterile environment.^{36,37} As a consequence, patients may develop fever or become septic. It is, however, not entirely clear how many patients develop such symptoms after an endoscopic transluminal drainage procedure. Additionally, the therapeutic consequences are unknown. Therefore, **Chapter 6**, describes a retrospective multicenter case series of patients who underwent endoscopic transluminal drainage for symptomatic sterile necrosis.

Part IV - Disruption of disconnection of the pancreatic duct

The fourth part of my thesis concerns a common complication following necrotizing pancreatitis. When patients develop necrosis of the pancreatic parenchyma, the main pancreatic duct is often damaged. As a result, the pancreatic duct may leak pancreatic secretions into the peritoneum. Such a leak might lead to recurrent pancreatic fluid collections or pancreatic ascites.^{4,5} This is also known as a partial pancreatic duct disruption or complete disconnection, depending on the extent of damage. This concerns approximately 10% to 30% of patients that develop necrotizing pancreatitis.^{4,6,7} To date, no guidelines on the best approach to treat this complication exist. It is also unknown whether

there is consensus among expert pancreatologists in the field. Therefore, **Chapter 7** investigates the opinion of a multidisciplinary expert group of pancreatologists in an international case vignette survey study.

Part V - Acute pancreatitis and COVID-19

In the fifth part of this thesis, we look further into a highly relevant and pressing topic, that marked the final period of my PhD trajectory, but also the lives of everyone worldwide. COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread around the world last year. At the start of the global pandemic, several studies reported on a possible association between COVID-19 and acute pancreatitis.³⁸⁻⁴⁰ SARS-CoV-2 enters the host cells via the ACE2 receptor.⁴¹ This receptor is also expressed in pancreatic ductal cells, making an association possible. Previous research demonstrated that 10 to 20% of patients with COVID-19 developed acute pancreatitis, but this does not necessarily mean that COVID-19 should be considered as a new aetiology for acute pancreatitis.^{40,42} Moreover, the presence of abdominal pain and imaging findings were often not specified in previous literature, which are crucial for diagnosing acute pancreatitis according to the revised Atlanta Classification.¹⁰ We therefore performed a cross-sectional study in which we evaluated how many admitted patients with COVID-19 developed acute pancreatitis according to the revised Atlanta criteria. The results of this study are described in **Chapter 8**.

Part VI - Concluding remarks

The main findings of this thesis are summarized and discussed in **Chapter 9** and **10**.

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