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REVIEW ARTICLE

Necrotizing Pancreatitis: A comprehensive review of the presentation, management, and complications

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Abstract

Necrotizing pancreatitis (NP) is a life-threatening complication of acute pancreatitis. It requires an extended hospital stay, aggressive management, and has a higher risk of mortality. Risk factors such as comorbidities in the patient's history including history of coronary artery disease and cerebrovascular disease can increase the risk of developing necrotizing pancreatitis. The presentation of necrotizing pancreatitis is similar to acute pancreatitis, but specific labs such as hematocrit level can be monitored to anticipate the development of necrotizing pancreatitis. In addition, diagnostic imaging must be obtained to classify necrotizing pancreatitis and aid in management choice. Fluid hydration, adequate pain management, and nutritional support are the principles of treating necrotizing pancreatitis. Deciding whether to drain the necrotic collection or not is usually determined based on the type of necrosis present and whether it is infected. Infected necrotizing pancreatitis can also occur, and patients usually need to be monitored closely with appropriate antibiotics for a long duration. Patients affected by necrotizing pancreatitis can potentially develop complications that can lead to devastating outcomes. Necrotizing pancreatitis complications can occur due to an inflammatory reaction on the adjacent structure such as splanchnic vein thrombosis, gastrointestinal fistula or inflammatory reaction within the pancreas leading to an exocrine and an endocrine pancreatic insufficiency. We present here a literature review of necrotizing pancreatitis and the complications that can arise from it.

INTRODUCTION

Necrotizing pancreatitis (NP) is an extreme complication of acute pancreatitis where part of the pancreas dies. necrotizing pancreatitis can develop in 10% of patients with acute pancreatitis. It is caused by premature activation of the pancreatic enzymes.[1] After the initial insult that follows acute pancreatitis, premature activation of trypsin leads to activating other enzymes released from the pancreas, such as protease, lipase, phospholipase, and elastase, which lead to autodigestion and inflammation locally that would result in cell death and form of necrotic tissues.[2,3] necrotizing pancreatitis is diagnosed on imaging such as computed tomography (CT) scan or magnetic resonance imaging (MRI). Therefore, patients who develop necrotizing pancreatitis should be monitored closely due to complications that can follow.

METHODS

To further investigate the diagnosis and management of necrotizing pancreatitis along with its complications, a systematic search through MEDLINE (PubMed), Google scholar, and OVID databases was conducted. Our study includes articles from 1977-2022. Reports were restricted only to the English language. The keywords acute pancreatitis, necrotizing pancreatitis, epidemiology, management, and complications were used. The information found in the selected articles were carefully evaluated prior to being included in our study. Relevant data from the initial gathered reports were cited in our study. Additionally, references from the retrieved papers were also reviewed for additional collection of reports.

EPIDEMIOLOGY

Acute pancreatitis is one of the most common gastrointestinal presentations to the emergency department.[4,5] In the United States, the incidence of acute pancreatitis is approximately 13-45 per 100,000 population.[6,7,8,9,10] It presents a significant public health burden with over 275,000 hospitalizations a year in the United States, accounting for the second-highest hospital stay cost (approximately 2.5 billion dollars per year).[11] A recent study showed that the overall mortality rate from acute pancreatitis is approximately 1% and stems mainly from associated complications.[6,7] In the United States, acute pancreatitis remains deadly with over 8000 deaths per year. A life-threatening complication of acute pancreatitis is necrotizing pancreatitis which can occur in 20% of patients presenting with acute pancreatitis.[12,13]

Necrotizing pancreatitis is uncommon but is associated with severe complications, extended hospital stays, life-threatening infections, and a high mortality rate. The two major causes of acute pancreatitis and, by extension, necrotizing pancreatitis are gallstone (40-48%) and alcohol consumption (24-27%).[4] Up to 60% of necrotizing pancreatitis can become infected.[14] The morbidity and mortality associated with acute pancreatitis are higher when necrosis is present, especially when the area of necrosis is also infected.[15] Generally, the mortality rate for sterile necrosis is up to 10%, while it increases to 20-30% when the necrotic region becomes infected (*Figure 1*).[4]

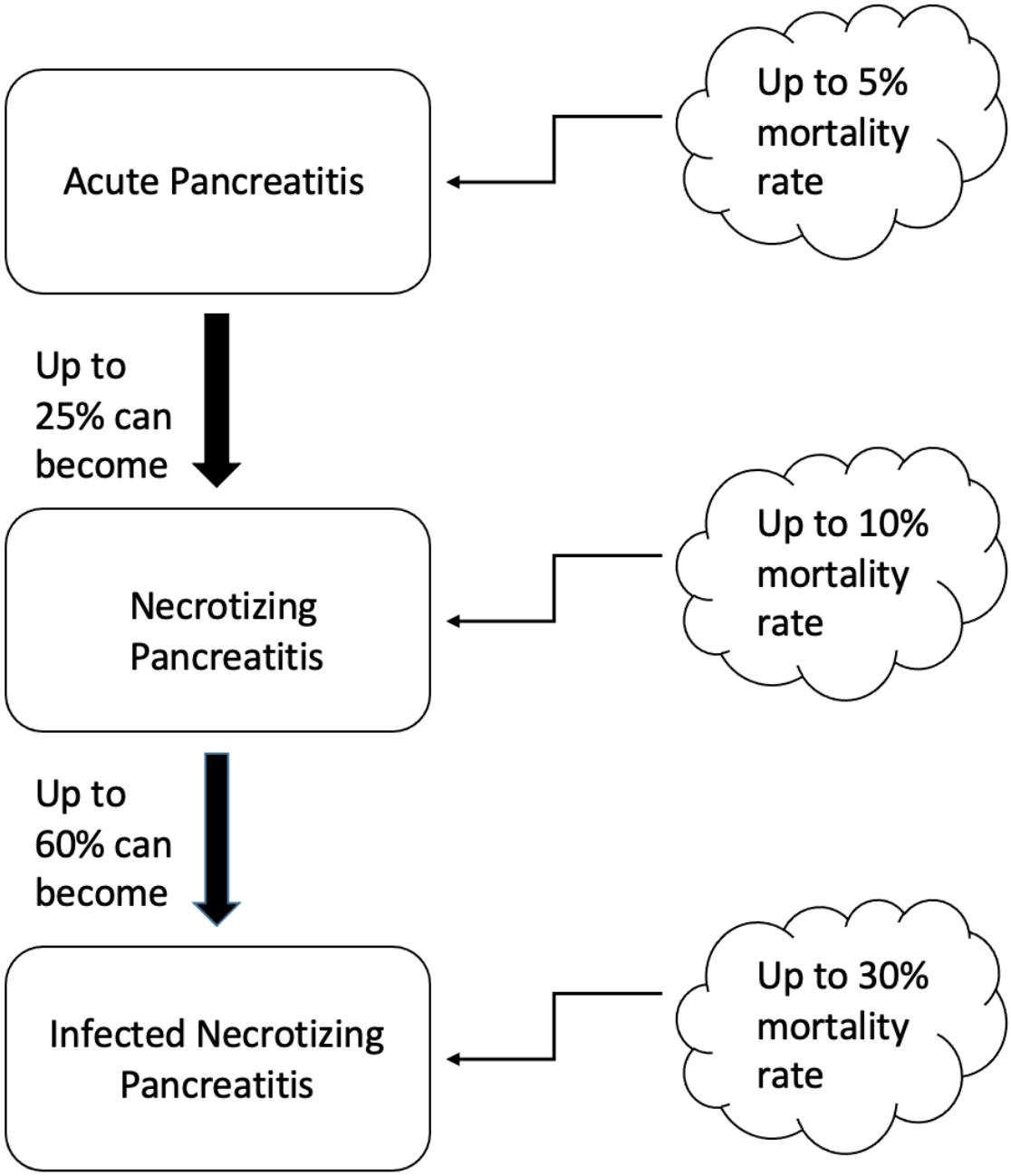

Figure 1. Mortality rate in acute, necrotizing, and infected necrotizing pancreatitis.

The mortality rate and prevalence of acute pancreatitis becoming necrotizing pancreatitis and infected necrotizing pancreatitis are depicted in this figure. Patients with infected necrotizing pancreatitis have the highest mortality rate followed by patients with necrotizing pancreatitis and last, patients with acute pancreatitis.[11,12,14]

RISK FACTORS

The patient's initial presentation to the hospital, labs, and imaging during

hospitalization can help identify a subset of patients at risk of developing necrotizing pancreatitis or even infected necrotizing pancreatitis (INP). This knowledge earlier in the course of hospitalization can help identify high-risk patients, can help take precautions that can mitigate the risk of development of necrotizing pancreatitis, and ultimately can help guide the course of medical, endoscopic, or surgical management.

Comorbidities in the patient's history, particularly coronary artery disease and cerebrovascular disease, can increase the risk of developing necrotizing pancreatitis.[16] Additional risk factors include the use of loop diuretics and somatostatins.[16] Multiple studies have demonstrated that patients presenting with elevated hematocrit (HCT) or failure of admission hematocrit level to decrease at approximately 24 hours post-admission were independent risk factors for the development of necrotizing pancreatitis (*Table 1*).[5,17,18]

Table 1. Factors associated with higher risk of developing NP on admission.

- Presence of comorbidities such as coronary artery disease and cerebrovascular accident.
- Use of loop diuretics and somatostatin.
- Elevated hematocrit level +/- failure to decrease level in the first 24 hours of admission.

Table 1. Factors associated with higher risk of developing necrotizing pancreatitis on admission.[5,16,17]

More importantly, if the level of HCT increases from 40% to 50%, or over 50% within the first 48 hours of admission, it could substantially increase the patient's risk of developing INP, which is associated with a higher mortality rate.[5] INP has been associated with more extended hospital stays and higher mortality rates.[19] Independent risk factors such as elevated lactate dehydrogenase (LDH), high computed tomography severity index (CTSI – sum of Balthazar score, which is a grading of pancreatitis, and pancreatic necrosis score), delayed fluid resuscitation, and hypoxemia has been associated with INP in patients with severe acute pancreatitis.[19] Patients presenting with LDH level > 1000 and CTSI > 5.5 compared to patients with LDH <500 and CTSI <3.13 have been associated with INP.[19] More importantly, delaying fluid resuscitation can significantly increase the risk of developing INP (*Table 2*).[18,19] Some labs can be obtained during the hospital stay to

determine whether a patient is at a higher risk of developing INP. A study has suggested that elevated D-dimer levels in the first few days after admission is associated with a higher risk of developing INP.[20]

Table 2: Factors associated with higher risk of developing INP on admission

- Elevated lactate dehydrogenase (LDH).
- High computed tomography serenity index (CTSI).
- Delayed fluid resuscitation.

Table 2. Factors associated with higher risk of developing INP on admission.[5,19,20]

A recent study in 2017 monitored labs of patients with necrotizing pancreatitis and found that the maximum levels of procalcitonin (PCT), C-reactive protein (CRP), hematocrit (HCT), and blood urea nitrogen (BUN) within 48 hours of admission are independent risk factors of developing INP.[5] More specifically, the increase of PCT level within 48 hours with a cut-off of 1.39 had an odds ratio of 2.559 (p-value 0.002).[5] In addition, the elevation of BUN by only 5mg/dL within 48 hours of admission was associated with developing INP.[21] The BISAP score (BUN >25 mg/dl, impaired mental status, systemic inflammatory response syndrome (SIRS), age > 60 years, or the presence of a pleural effusion) was developed in 2008 as a simple and valid method for identifying patients at increased risk of in-hospital mortality.[22]

In conclusion, patients with comorbidities, the use of loop diuretics or somatostatins, admission HCT level of > 47% on admission are at higher risk of developing necrotizing pancreatitis. On the other hand, patients presenting with elevated LDH, high CTSI, delayed fluid resuscitation, and hypoxemia have a higher risk of developing INP. Elevated D-dimer levels, HCT, BUN, CRP, and PCT within 48 hours of admission are independent factors associated with a higher risk of developing INP.

PRESENTATION & DIAGNOSIS

Necrotizing pancreatitis can occur as a complication post-pancreatitis. Therefore, symptoms and presentation of necrotizing pancreatitis resemble symptoms of acute/chronic pancreatitis in terms of unbearable pain in the upper region of the abdomen. Symptoms such as nausea, fever, vomiting, dehydration, rapid heart rate, and abdominal bloating can also occur (23, 24). Two distinctive signs may be noted as the pancreatic tissue starts to die and bleeding increases. Grey Turner's sign manifests as ecchymosis or discoloration of the flank area, while Cullen's sign exhibits edema and

bruising around the umbilicus (25). Diagnosing necrotizing pancreatitis is based mainly on imaging findings (26), with CT scan being the primary imaging modality. Ideally, imaging should be performed after 3-5 days of patient presentation to the hospital to determine whether necrosis is present (27). MRI can be used in select patients (26). Imaging can delineate the extent and severity of necrotizing pancreatitis based on the revised Atlanta classification (27). The revised Atlanta classification system divides pancreatic necrosis into three morphologic subtypes, depending on whether it involves only peripancreatic tissue, pancreatic parenchyma, or both (28). The severity of necrotizing pancreatitis is based on the extent of parenchymal involvement by necrosis (<30%, 30-50%, or >50%) (27). The revised Atlanta classification subdivides collections of necrosis according to the time of disease onset. Within four weeks of the onset of pancreatitis, it is defined as an acute necrotic collection, whereas persistence of fluid collection beyond four weeks is termed as walled-off necrosis (*Figure 2*).

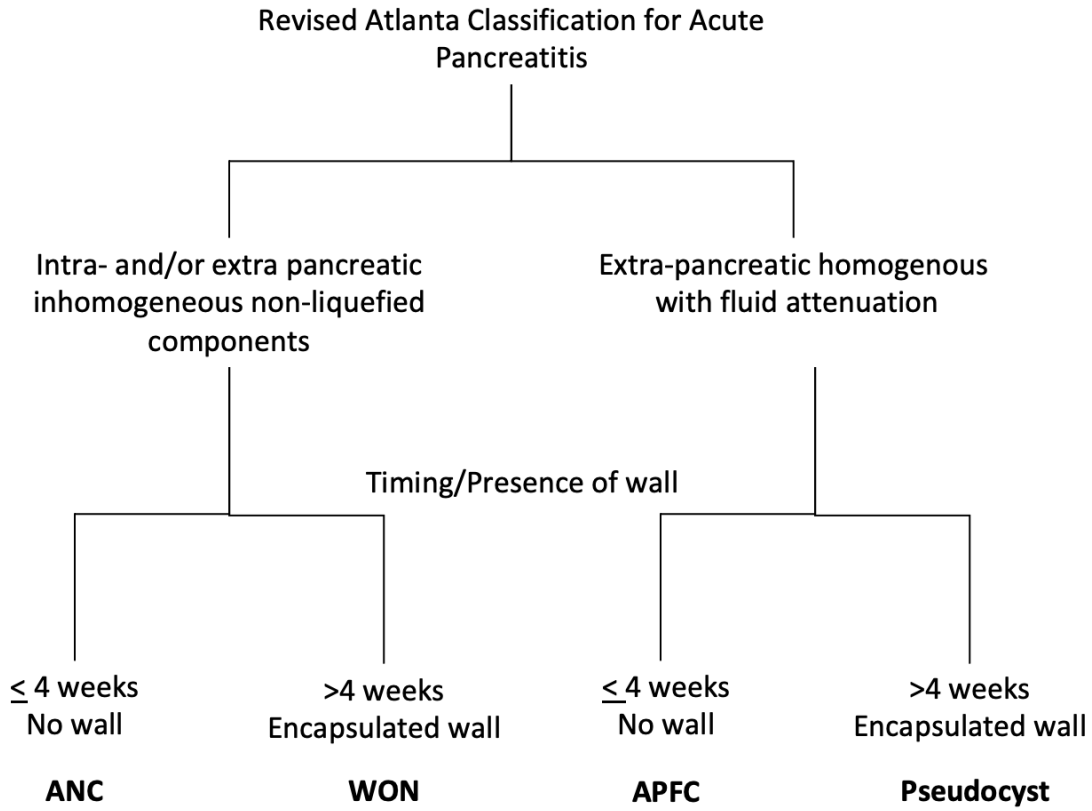

Figure 2. Classification of pancreatic fluid collection. ANC = Acute necrotic collection, APFC = acute peripancreatic fluid collection, WON = walled-off necrosis.

Pancreatic fluid collection can be divided into four distinct collection subtypes based on fluid location, fluid components, time elapsed since the onset of pancreatitis, and whether fluid is encapsulated with a wall or not. The presence of fluid only indicates fluid collection

due to interstitial edematous pancreatitis which can be subdivided into APFC or Pseudocyst depending on the time elapsed since the onset of pancreatitis. On the other hand, the presence of non-liquefied components indicates fluid collection due to necrotic pancreatitis which can be subdivided into ANC and WON depending on the time elapsed since the onset of pancreatitis. *References (7, 18, 26-28)*

MANAGEMENT

The first step in managing AP is aggressive fluid hydration followed by adequate pain management, and nutritional support as tolerated (*Figure 3*).

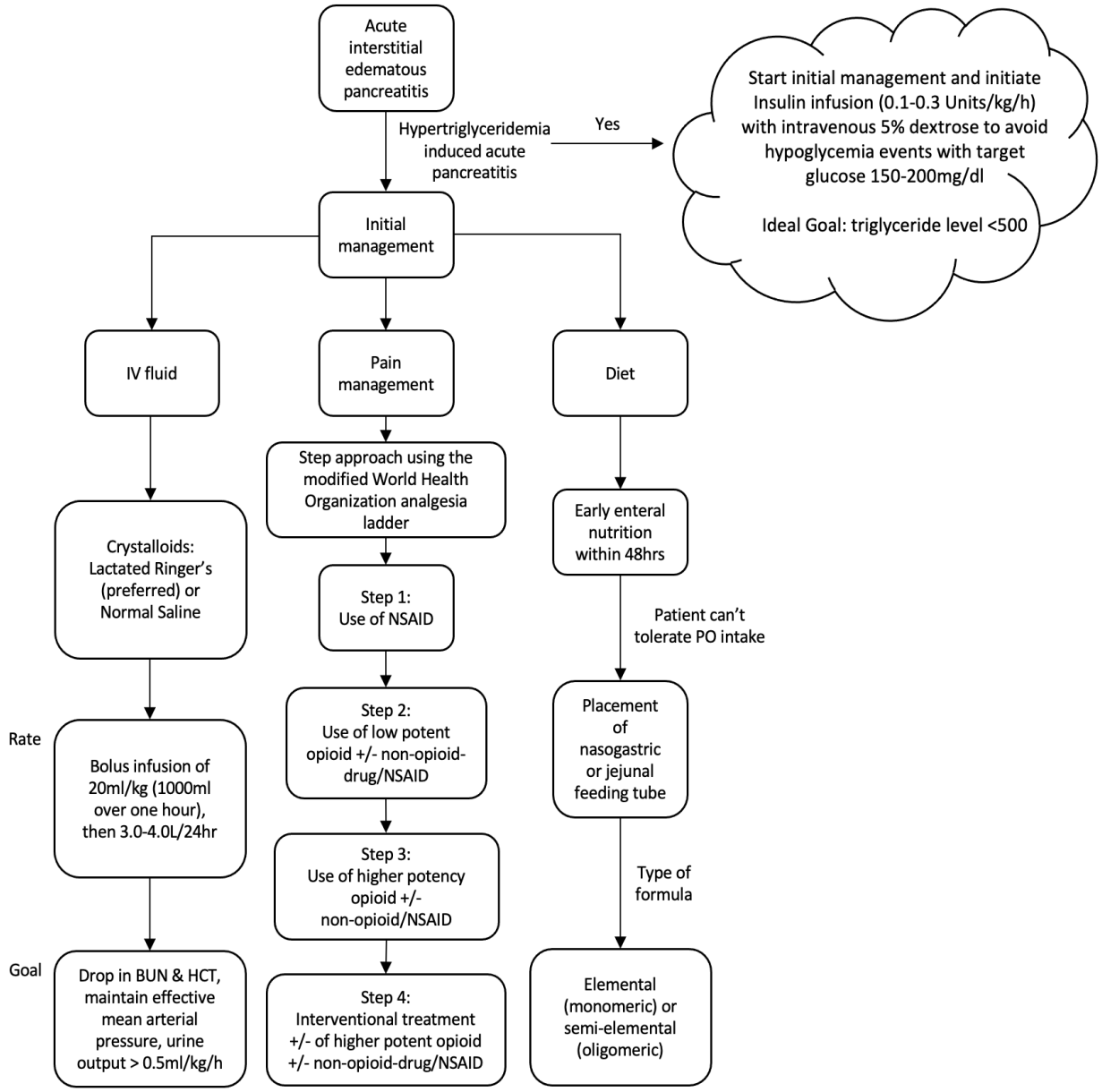

Figure 3. Management of acute pancreatitis.

Different societies of medicine present different yet similar generalized guidelines for management of acute interstitial edematous pancreatitis. Patients with hypertriglyceridemia induced acute pancreatitis are treated with insulin infusion. Patients with acute interstitial edematous pancreatitis due to other etiologies are managed mainly by IV fluid, pain management, and early enteral nutrition intake. Aggressive fluid resuscitation with a goal of HCT and BUN drop, and more than 0.5 ml/kg/h urine output has been the standard treatment. Pain management using modified World health Organization analgesia ladder has proven to be beneficial and adequate. Early feeding is supported as is thought to help protect the gut-mucosal barrier and reduce bacterial translocation.[4,7,11,18,19,21]

The American College of Gastroenterology (ACG) pancreatitis guidelines and the American Gastroenterological Association (AGA) clinical guidance recommend early aggressive intravenous (IV) fluid hydration.[18,19] Despite prior randomized trials, no medical intervention except for early IV fluid resuscitation has been demonstrated to be effective in the management of acute pancreatitis.[29,30,31] This aids with circulatory support to prevent serious complications. While the AGA guidance makes no recommendation whether normal saline or lactate ringer's (LR) should be used, a prior study.[32] demonstrated some benefit as the preferred isotonic crystalloid solution. Theoretically, low pH would activate trypsinogen leading to acinar cells being more susceptible to injury. As normal saline can lead to non-anion gap hyperchloremic metabolic acidosis, therefore lowering pH, a more pH balanced LR would prevent activation of trypsinogen essentially limiting the severity of pancreatitis.[32,33] Based on this, the ACG guidelines published in 2013 suggest the use of LR as the initial choice of fluids. However, there is a shift in current paradigm of management as continued aggressive hydration has not been shown to have benefit and may have worse outcomes.[34,35,36] A recently published randomized clinical trial (WATERFALL trial) demonstrated that early aggressive fluid resuscitation resulted in higher incidence of fluid overload without improvement in clinical outcomes.[37] With this paradigm shift, the ACG is currently in the process of updating its guidelines on acute pancreatitis with expected publication in 2023.

Despite adequate fluid hydration, if necrotizing pancreatitis develops, continued IV fluids and pain management are necessary as patients tend to have worsening abdominal pain. In addition, adequate nutritional support is critical in necrotizing pancreatitis patients, as a lack of nutritional support is associated with high mortality.[38] Whether to drain the necrotic collection depends on the type of necrosis present and whether it is infected (*Figure 4*). Intervention is usually deferred until after four to six weeks to allow for maturation of the pancreatic necrosis.[39,40] Traditionally, the only viable approach was open surgical transgastric necrosectomy (TGN). Recently, other approaches have been adopted, such as image-guided percutaneous drainage, endoscopic transmural drainage, endoscopic necrosectomy, video-assisted retroperitoneal

debridement (VARD), and laparoscopic approaches. The concept of using a minimally invasive approach with limited debridement and spaced-out operations has been shown to reduce the likelihood of causing significant bleeding or resecting viable parenchyma.[39]

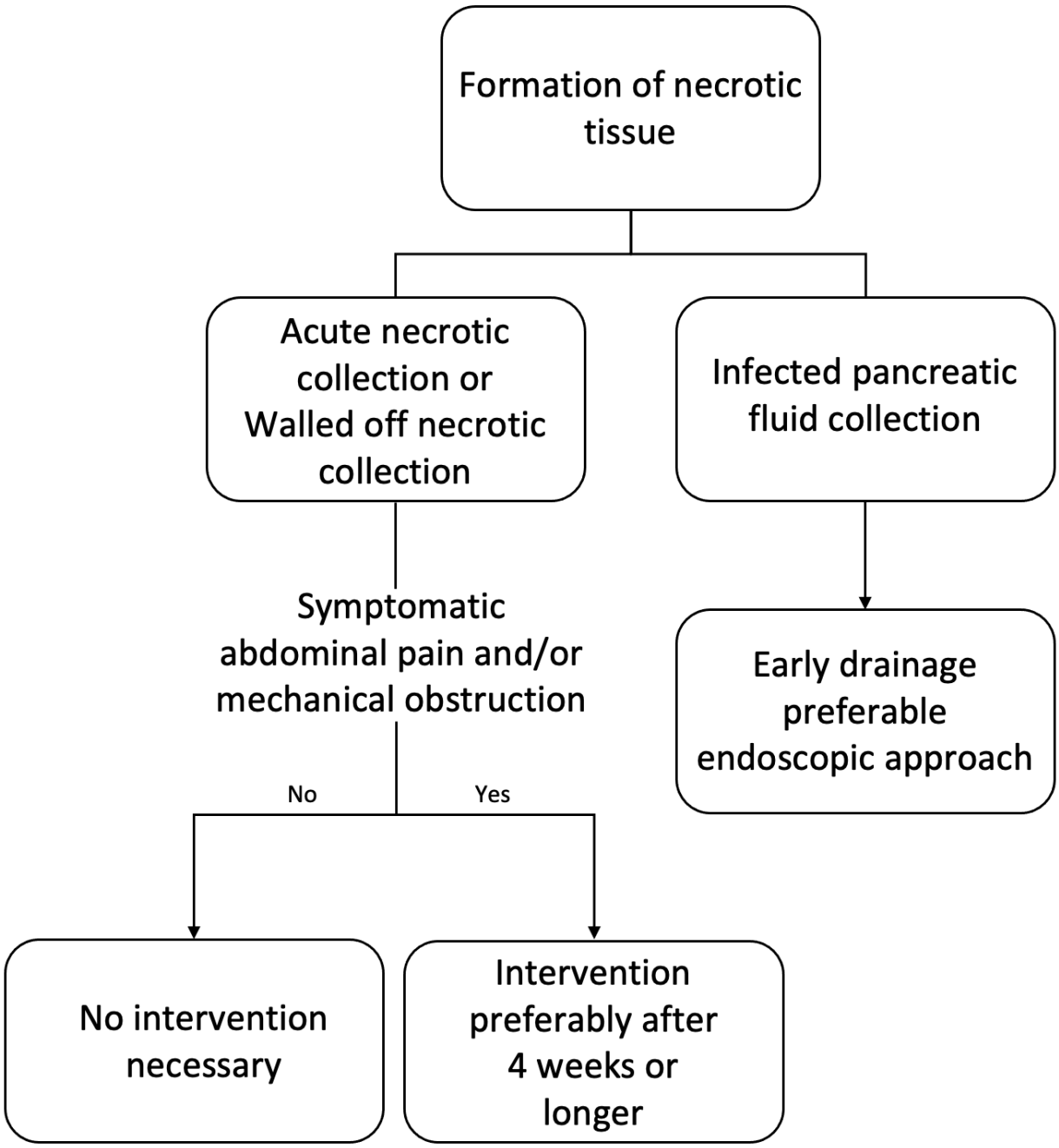

Figure 4. Management of necrotic tissue formation

The formation of necrotic tissue collection requires further evaluation and possible intervention depending on whether the fluid collection is causing symptoms, obstruction and/or infected. If the necrotic fluid is infected, early drainage is preferable as it is

associated with lower mortality rate. If the necrotic fluid not infected but is causing symptoms such as abdominal pain, or causing obstruction, recommendation is to drain the fluid but preferable wait 4 weeks or longer for encapsulated wall formation. No intervention is necessary if the necrotic fluid collection is not causing any symptoms, obstruction, and is not infected.[39,40,41,43]

A recent study comparing endoscopic versus surgical treatment for INP found that the endoscopic approach is associated with lower odds of experiencing new onset multiorgan failure and were less likely to suffer from perforation of the visceral organ or forming pancreatic fistula and had significantly decreased hospital stay. However, there was no difference in mortality rate.[41] Therefore, the role of open necrosectomy has expectedly declined from its historical prevalence because of the success of minimally invasive techniques for pancreatic debridement and improvement in critical care.[39] Image-guided, endoscopic, and minimally invasive approaches seem to be favored over open surgery but deciding which of these approaches is better is another challenge. Percutaneous catheter drainage for initial treatment is a safe and effective technique for treating acute INP.[42] An endoscopic drainage approach can effectively drain and uncomplicated pseudocyst.[43]

On the other hand, walled-off necrosis typically requires mechanical debridement. A minimally invasive surgical approach offers some advantages over endoscopy in creating a larger cystogastrostomy, allowing concurrent intra-abdominal procedures such as cholecystectomy, and facilitating management of complications such as perforation or hemorrhage.[44,45] As of now, many suggest that open pancreatic debridement is considered the final step in the treatment paradigm of necrotizing pancreatitis, but there are still numerous patients that require it.[11,46]

ANTIBIOTIC PROPHYLAXIS

Most patients with necrotizing pancreatitis would fulfill SIRS or sepsis criteria. Hence, admitting teams are prone to prescribing prophylactic antibiotics. ACG recommends against routine use of prophylactic antibiotics in severe acute pancreatitis and sterile necrosis.[18] Nevertheless, if a patient presents with sepsis or there is a high suspicion of IPN, antibiotics should be initiated immediately with imaging and tissue samples obtained as soon as possible.[47] However, antibiotics should be discontinued once infection is ruled out by tissue sample and imaging.[18] A trove of studies did not show a statistically significant difference in the early administration of prophylactic antimicrobials in patients with acute necrotizing pancreatitis in terms of infection rate, mortality, systemic complications, or requirement for surgical intervention.[48,49,50,51,52]

COMPLICATIONS

Necrotizing pancreatitis itself is a complication of acute pancreatitis. However, some complications follow necrotizing pancreatitis that clinicians should be aware of to manage their patients optimally. Disconnected pancreatic duct syndrome (DPDS), splanchnic vein thrombosis, new

endocrine or exocrine pancreatic insufficiency, symptomatic chronic pancreatitis, incisional hernias, chronic pain syndrome, pancreatic duct stricture, bile duct stricture, gastrointestinal fistula, presinusoidal portal hypertension, and duodenal stricture are all complications that can follow necrotizing pancreatitis.[53] These complications in necrotizing pancreatitis survivors are common; therefore, an experienced physician should follow these patients long-term.[53]

In a recent study of 570 patients, new endocrine or exocrine pancreatic insufficiency occurred in 45% of patients, with endocrine insufficiency occurring twice as often as exocrine insufficiency. In the same study, it was also found that disconnected pancreatic duct syndrome was diagnosed in 49% of patients, and it had a higher incidence in patients with necrosis involving the neck of the pancreas. In addition, out of the 570 patients diagnosed with necrotizing pancreatitis, 257 (approximately 45%) had developed splanchnic vein thrombosis. It was predominantly noted in patients with a higher degree of gland necrosis and higher CTSI. Duodenal complications such as duodenal fistula and duodenal stricture can occur in up to 6% of patients with necrotizing pancreatitis.[54] Colonic complications including localized ileus with pseudo-obstruction, obstruction, hemorrhage, necrosis, fistula, and colon ischemia, can also occur in up to 15% in patients with necrotizing pancreatitis.[55] Infrequent but reported complications of necrotizing pancreatitis include chylous ascites, cystic-duodenal fistula, emphysematous pancreatitis, hemorrhagic necrotizing pancreatitis, and necrotizing fasciitis of the abdominal wall.[56,57,58,59,60]

Disconnected pancreatic duct syndrome:

In DPDS, there is a lack of main duct continuity between viable secreting pancreatic tissue and the gastrointestinal tract secondary to ductal necrosis.[60] Patients with necrotizing pancreatitis can develop DPDS due to ductal necrosis obstructing the main pancreatic duct. The viable pancreatic tissue continues to secrete pancreatic juice that is not drained to the gastrointestinal tract, leading to recurrent pancreatic fluid collection. Diagnosing DPDS can be done via ERCP or EUS, demonstrating the main pancreatic duct cut-off or discontinuity with the inability to access or cannulate the upstream pancreatic duct.[60,61] Treatment of DPDS consists of multiple approaches such as endoscopic placement of a transpapillary or transgastric stent to drain the pseudocyst and the proximal duct.[61] Removal of the non-viable disconnected pancreatic segment or creating a pancreaticojejunostomy to drain the viable segment can also be done.[60] Cross-sectional imaging modalities, i.e. CT or MRI with contrast, can help localize the pancreatic duct disruption point.[61]

Splanchnic vein thrombosis:

Splanchnic vein thrombosis (SVT) is another complication associated with severe pancreatitis and may involve the portal vein, splenic vein, or superior mesenteric vein, either in combination or separately.[62] It occurs in less than one-fourth of patients affected by severe pancreatitis. Thrombosis of any of these vessels results due to the anatomic

location of these veins along the entire posterior aspect of the pancreas, where it lies in direct contact with peripancreatic inflammatory tissue.[62,63] This can lead to portal hypertension with development of gastroesophageal varices or isolated gastric varices, and in some instances, hypersplenism.[62] A Doppler ultrasound of the abdomen or an abdominal CT scan is used for diagnosis. Confirmation often can be made by CT angiography or MR venography.[63] Although treatment of pancreatitis-induced splanchnic vein thrombosis is primarily directed towards management of the pancreatitis, there is some role for anticoagulation in this setting. However, there are no guidelines currently for anticoagulation of SVT due to pancreatitis. The suggestions for anticoagulation are extrapolated from data of anticoagulation in the setting of extrahepatic portal vein thrombosis, or mesenteric thrombosis.[64,65] Current consensus is to treat symptomatic patients with anticoagulation while asymptomatic patients should be clinically observed, followed by serial doppler ultrasound of the abdomen.[66] In rare cases, ultimate management of symptomatic patients would include splenectomy.[62,67]

Endocrine pancreatic insufficiency:

The endocrine function of the pancreas is to secrete hormones such as glucagon and insulin. Endocrine insufficiency can develop due to progressive gland destruction, ongoing inflammatory burden, and tissue necrosis.[68] It is usually diagnosed in patients who present with hyperglycemia or develop new-onset diabetes with a history of chronic pancreatitis. This is termed as type 3c diabetes.[69] Ewald and Bretzel proposed the following primary criteria for diagnosis of type 3c diabetes.[70]:

1. Exocrine pancreatic insufficiency (by monoclonal fecal elastase-1 testing or direct function tests),
2. Imaging (EUS, MRI, or CT scan) consistent with pancreatic abnormalities, and
3. Absence of type 1 diabetes related autoimmune markers.

It can also lead to low glycogen production and hypoglycemia symptoms as well. Treatment includes close management of diabetes and its complications.

Exocrine pancreatic insufficiency:

Exocrine pancreatic insufficiency (EPI) refers to a lack of enzymes secreted by the pancreas, leading to dietary malabsorption. Exocrine pancreatic enzyme deficiency, such as amylase, protease, and lipase, results in the inability to digest food properly. It is due to a loss of acinar cells following necrotizing pancreatitis, acinar cell fibrosis due to persistent inflammation, and the diminished production of exocrine enzymes from residual viable acinar cell colonies. Patients usually present with symptoms of flatulence, steatorrhea, and malnutrition. Exocrine insufficiency can be diagnosed with measurement of fecal fat excretion of > 7 g/day on a 100 g/day of fat in the diet of patients with history of necrotizing pancreatitis[71] and low fecal elastase.[72] Treatment options include pancreatic enzyme replacement therapy to compensate for deficiencies in endogenous enzyme secretion.[73]

Gastrointestinal fistula:

A gastrointestinal fistula is a well-recognized complication of NP/INP. It may involve the stomach, small intestine, or colon depending on the site of fistula formation. Most GI fistulas involve the colon, followed by the duodenum. It can occur due to direct erosion from digestive enzymes released by the inflamed pancreas into the adjacent GI tract[74], or as a sequela of intestinal necrosis secondary to vascular thrombosis in a region of inflammation and/or infection.[74,75] Most GI fistula could close spontaneously with nonsurgical management over time, however, approximately 70% of colonic fistula could require surgical intervention with enterostomy.[75] With the advancement in therapeutic endoscopy, endoscopic closure of pancreatitis-induced GI fistula could be attempted depending on the site of the fistula.[76] Although a complication in INP, a GI fistula could potentially benefit a patient by allowing drainage of the infected necrosis into the GI tract.[75,77,78]

CONCLUSION

Patients with necrotizing pancreatitis have a higher mortality rate and require a longer hospital stay. Specific physical exam abnormalities and labs have been linked to developing necrotizing pancreatitis in patients diagnosed with acute pancreatitis. The administration of antibiotics in sterile necrotizing pancreatitis is not supported and antibiotics should be limited to patients with a high suspicion of INP. In general, the use of less invasive interventions in the management of necrotizing pancreatitis over the last few years have led to improved outcomes.

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References:

1. Wrobleski DM, Barth MM, Oyen LJ. Necrotizing pancreatitis: pathophysiology, diagnosis, and acute care management. AACN Clin Issues. 1999;10(4):464-77.

2. Alvi AR, Sheikh GM, Kazim SF. Delayed surgical therapy reduces mortality in patients with acute necrotizing pancreatitis. J Pak Med Assoc. 2011;61(10):973-7.

3. Johnstone C. Pathophysiology and nursing management of acute pancreatitis. Nurs Stand. 2018.

4. Boumitri C, Brown E, Kahaleh M. Necrotizing Pancreatitis: Current Management and Therapies. Clin Endosc. 2017;50(4):357-65.

5. Chen HZ, Ji L, Li L, Wang G, Bai XW, Cheng CD, et al. Early prediction of infected pancreatic necrosis secondary to necrotizing pancreatitis. Medicine (Baltimore). 2017; 96(30):e7487.

6. Wang GJ, Gao CF, Wei D, Wang C, Ding SQ. Acute pancreatitis: etiology and common pathogenesis. World J Gastroenterol. 2009; 15(12):1427-30.

7. Forsmark CE, Vege SS, Wilcox CM. Acute Pancreatitis. N Engl J Med. 2016; 375(20):1972-81.

8. Das S, Mahakkanukrauh P, Ho CC. The Burden of Gastrointestinal, Liver, and Pancreatic Diseases: The Global Scenario. Gastroenterology. 2016;150(4):1045-6.

9. Peery AF, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology. 2012; 143(5):1179-87.e3.

10. Peery AF, Crockett SD, Barritt AS, Dellon ES, Eluri S, Gangarosa LM, et al. Burden of Gastrointestinal, Liver, and Pancreatic Diseases in the United States. Gastroenterology. 2015;149(7):1731-41.e3.

11. Roch AM, Maatman T, Carr RA, Easler JJ, Schmidt CM, House MG, et al. Evolving treatment of necrotizing pancreatitis. Am J Surg. 2018;215(3):526-9.

12. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.

13. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362(16):1491-502.

14. Phogat D, Bajpai M, Agrawal P, Ganguli P. Acute necrotizing pancreatitis. Autops Case Rep. 2020;10(4):e2020215.

15. Baron TH, Morgan DE. Acute necrotizing pancreatitis. N Engl J Med. 1999; 340(18):1412-7.

16. Chao CT, Chao JY. Case report: furosemide and pancreatitis: Importance of dose and latency period before reaction. Can Fam Physician. 2013;59(1):43-5.

17. Baillargeon JD, Orav J, Ramagopal V, Tenner SM, Banks PA. Hemoconcentration as an early risk factor for necrotizing pancreatitis. Am J Gastroenterol. 1998;93(11):2130-4.

18. Tenner S, Baillie J, DeWitt J, Vege SS, Gastroenterology ACo. American College of Gastroenterology guideline: management of

acute pancreatitis. Am J Gastroenterol. 2013;108(9):1400-15; 16.

19. Zeng YB, Zhan XB, Guo XR, Zhang HG, Chen Y, Cai QC, et al. Risk factors for pancreatic infection in patients with severe acute pancreatitis: an analysis of 163 cases. J Dig Dis. 2014;15(7):377-85.

20. Ji L, Lv JC, Song ZF, Jiang MT, Li L, Sun B. Risk factors of infected pancreatic necrosis secondary to severe acute pancreatitis. Hepatobiliary Pancreat Dis Int. 2016;15(4):428-33.

21. Talukdar R, Nechutova H, Clemens M, Vege SS. Could rising BUN predict the future development of infected pancreatic necrosis? Pancreatology. 2013;13(4):355-9.

22. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early prediction of mortality in acute pancreatitis: a large population-based study. Gut. 2008;57(12):1698-703.

23. Harris HW, Barcia A, Schell MT, Thoeni RF, Schecter WP. Necrotizing pancreatitis: a surgical approach independent of documented infection. HPB (Oxford). 2004;6(3):161-8.

24. Tran A, Fernando SM, Rochwerg B, Inaba K, Bertens KA, Engels PT, et al. Prognostic factors associated with development of infected necrosis in patients with acute necrotizing or severe pancreatitis-A systematic review and meta-analysis. J Trauma Acute Care Surg. 2022;92(5):940-8.

25. Chung KM, Chuang SS. Cullen and Grey Turner signs in idiopathic perirenal hemorrhage. CMAJ. 2011;183(16):E1221.

26. Shyu JY, Sainani NI, Sahni VA, Chick JF, Chauhan NR, Conwell DL, et al. Necrotizing pancreatitis: diagnosis, imaging, and intervention. Radiographics. 2014;34(5):1218-39.

27. Manfredi R, Brizi MG, Canadè A, Vecchioli A, Marano P. Imaging of acute pancreatitis. Rays. 2001;26(2):135-42.

28. Thoeni RF. The revised Atlanta classification of acute pancreatitis: its importance for the radiologist and its effect on treatment. Radiology. 2012;262(3):751-64.

29. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, Committee AGAICG. American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis. Gastroenterology. 2018; 154(4):1096-101.

30. Steinberg W, Tenner S. Acute pancreatitis. N Engl J Med. 1994;330(17):1198-210.

31. Banks PA, Freeman ML, Gastroenterology PPCotACo. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101(10):2379-400.

32. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. Clin Gastroenterol Hepatol. 2011;9(8):710-7.e1.

33. Gardner TB, Vege SS, Pearson RK, Chari ST. Fluid resuscitation in acute pancreatitis. Clin Gastroenterol Hepatol. 2008;6(10):1070-6.

34. Hjortrup PB, Haase N, Bundgaard H, Thomsen SL, Winding R, Pettilä V, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial

management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med. 2016;42(11):1695-705.

35. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care. 2015;19(1):251.

36. Malbrain ML, Marik PE, Witters I, Cordemans C, Kirkpatrick AW, Roberts DJ, et al. Fluid overload, de-resuscitation, and outcomes in critically ill or injured patients: a systematic review with suggestions for clinical practice. Anaesthesiol Intensive Ther. 2014; 46(5):361-80.

37. de-Madaria E, Buxbaum JL, Maisonneuve P, García García de Paredes A, Zapater P, Guilabert L, et al. Aggressive or Moderate Fluid Resuscitation in Acute Pancreatitis. N Engl J Med. 2022;387(11):989-1000.

38. Goodgame JT, Fischer JE. Parenteral nutrition in the treatment of acute pancreatitis: effect on complications and mortality. Ann Surg. 1977;186(5):651-8.

39. Pickens RC, Sulzer JK, Cochran A, Vrochides D, Martinie JB, Baker EH, et al. Retrospective Validation of an Algorithmic Treatment Pathway for Necrotizing Pancreatitis. Am Surg. 2019;85(8):840-7.

40. Driedger M, Zyromski NJ, Visser BC, Jester A, Sutherland FR, Nakeeb A, et al. Surgical Transgastric Necrosectomy for Necrotizing Pancreatitis: A Single-stage Procedure for Walled-off Pancreatic Necrosis. Ann Surg. 2020;271(1):163-8.

41. Haney CM, Kowalewski KF, Schmidt MW, Koschny R, Felinska EA, Kalkum E, et al. Endoscopic versus surgical treatment for infected necrotizing pancreatitis: a systematic review and meta-analysis of randomized controlled trials. Surg Endosc. 2020; 34(6):2429-44.

42. Freeny PC, Hauptmann E, Althaus SJ, Traverso LW, Sinanan M. Percutaneous CT-guided catheter drainage of infected acute necrotizing pancreatitis: techniques and results. AJR Am J Roentgenol. 1998; 170(4):969-75.

43. Varadarajulu S, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. Gastroenterology. 2013;145(3):583-90.e1.

44. Kirks RC, Sola R, Iannitti DA, Martinie JB, Vrochides D. Robotic transgastric cystgastrostomy and pancreatic debridement in the management of pancreatic fluid collections following acute pancreatitis. J Vis Surg. 2016;2:127.

45. Simo KA, Niemeyer DJ, Swan RZ, Sindram D, Martinie JB, Iannitti DA. Laparoscopic transgastric endolumenal cystogastrostomy and pancreatic debridement. Surg Endosc. 2014;28(5):1465-72.

46. Maatman TK, Zyromski NJ. Open Pancreatic Debridement in Necrotizing Pancreatitis. J Gastrointest Surg. 2021; 25(1):331-2.

47. Garret C, Canet E, Corvec S, Boutoille D, Péron M, Archambeaud I, et al. Impact of prior antibiotics on infected pancreatic necrosis microbiology in ICU patients: a retrospective cohort study. Ann Intensive Care. 2020;10(1):82.

48. Bai Y, Gao J, Zou DW, Li ZS. Prophylactic antibiotics cannot reduce infected pancreatic necrosis and mortality in acute necrotizing pancreatitis: evidence from a meta-analysis of randomized controlled trials. Am J Gastroenterol. 2008;103(1):104-10.

49. Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N, et al. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. Gastroenterology. 2004; 126(4):997-1004.

50. Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: a randomized, double-blind, placebo-controlled study. Ann Surg. 2007;245(5):674-83.

51. García-Barrasa A, Borobia FG, Pallares R, Jorba R, Poves I, Busquets J, et al. A double-blind, placebo-controlled trial of ciprofloxacin prophylaxis in patients with acute necrotizing pancreatitis. J Gastrointest Surg. 2009; 13(4):768-74.

52. Besselink MG, van Santvoort HC, Buskens E, Boermeester MA, van Goor H, Timmerman HM, et al. Probiotic prophylaxis in predicted severe acute pancreatitis: a randomised, double-blind, placebo-controlled trial. Lancet. 2008;371(9613):651-9.

53. Maatman TK, Roch AM, Ceppa EP, Easler JJ, Gromski MA, House MG, et al. The continuum of complications in survivors of necrotizing pancreatitis. Surgery. 2020; 168(6):1032-40.

54. Seligson U, Ihre T, Lundh G. Prognosis in acute haemorrhagic, necrotizing pancreatitis. Acta Chir Scand. 1982;148(5):423-9.

55. Sandrasegaran K, Tann M, Jennings SG, Maglinte DD, Peter SD, Sherman S, et al. Disconnection of the pancreatic duct: an important but overlooked complication of severe acute pancreatitis. Radiographics. 2007;27(5):1389-400.

56. Santos MA, Bose PS, Maher S, Desai M. Chylous Ascites: An Unusual Complication of Necrotizing Pancreatitis. Am J Med. 2017;130(4):e151-e2.

57. Kaistha S, Kumar A, Ramakrishnan TS. Necrotizing Fasciitis: A Rare Complication of Acute Necrotizing Pancreatitis. J Clin Diagn Res. 2017;11(6):PD05-PD6.

58. Di Mitri R, Amata M, Scimeca D, Bonaccorso A, Conte E, Lo Mastro M, et al. Cystoduodenal fistula: unusual complication after acute necrotizing pancreatitis with collection. Endoscopy. 2021;53(7):E247-E8.

59. Niryinganji R, Mountassir C, Siwane A, Tabakh H, Touil N, Kacimi O, et al. Emphysematous Pancreatitis: A Rare Complication of Acute Necrotizing Pancreatitis. Eur J Case Rep Intern Med. 2020;7(6):001550.

60. Verma S, Rana SS. Disconnected pancreatic duct syndrome: Updated review on clinical implications and management. Pancreatology. 2020;20(6):1035-44.

61. Alsaad AA, Dhannoon SM, Phillips MB. Disconnected pancreatic duct syndrome: a multidisciplinary management dilemma. BMJ Case Rep. 2016;2016.

62. Nadkarni NA, Khanna S, Vege SS. Splanchnic venous thrombosis and pancreatitis. Pancreas. 2013;42(6):924-31.

63. Agarwal AK, Raj Kumar K, Agarwal S, Singh S. Significance of splenic vein thrombosis in chronic pancreatitis. Am J Surg. 2008;196(2):149-54.

64. Garcia-Pagán JC, Hernández-Guerra M, Bosch J. Extrahepatic portal vein thrombosis. Semin Liver Dis. 2008;28(3):282-92.

65. Hall TC, Garcea G, Metcalfe M, Bilku D, Dennison AR. Management of acute non-cirrhotic and non-malignant portal vein thrombosis: a systematic review. World J Surg. 2011;35(11):2510-20.

66. Ageno W, Beyer-Westendorf J, Garcia DA, Lazo-Langner A, McBane RD, Paciaroni M. Guidance for the management of venous thrombosis in unusual sites. J Thromb Thrombolysis. 2016;41(1):129-43.

67. Sakorafas GH, Sarr MG, Farley DR, Farnell MB. The significance of sinistral portal hypertension complicating chronic pancreatitis. Am J Surg. 2000;179(2):129-33.

68. Diéguez-Castillo C, Jiménez-Luna C, Martín-Ruiz JL, Martínez-Galán J, Prados J, Torres C, et al. Role of Exocrine and Endocrine Insufficiency in the Management of Patients with Chronic Pancreatitis. J Clin Med. 2020;9(6).

69. Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016;1(3):226-37.

70. Ewald N, Bretzel RG. Diabetes mellitus secondary to pancreatic diseases (Type 3c)--are we neglecting an important disease? Eur J Intern Med. 2013;24(3):203-6.

71. Capurso G, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. Clin Exp Gastroenterol. 2019;12:129-39.

72. Struyvenberg MR, Martin CR, Freedman SD. Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC Med. 2017;15(1):29.

73. Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM. Less common etiologies of exocrine pancreatic insufficiency. World J Gastroenterol. 2017;23(39):7059-76.

74. Doberneck RC. Intestinal fistula complicating necrotizing pancreatitis. Am J Surg. 1989;158(6):581-3; discussion 3-4.

75. Jiang W, Tong Z, Yang D, Ke L, Shen X, Zhou J, et al. Gastrointestinal Fistulas in Acute Pancreatitis With Infected Pancreatic or Peripancreatic Necrosis: A 4-Year Single-Center Experience. Medicine (Baltimore). 2016;95(14):e3318.

76. Ito K, Igarashi Y, Mimura T, Kishimoto Y, Kamata I, Kobayashi S, et al. Severe Acute Pancreatitis with Complicating Colonic Fistula Successfully Closed Using the Over-the-Scope Clip System. Case Rep Gastroenterol. 2013;7(2):314-21.

77. Levy I, Ariche A. Complete recovery after spontaneous drainage of pancreatic abscess into the stomach. Scand J Gastroenterol. 1999;34(9):939-41.

78. Kochhar R, Jain K, Gupta V, Singhal M, Kochhar S, Poornachandra KS, et al. Fistulization in the GI tract in acute pancreatitis. Gastrointest Endosc. 2012; 75(2):436-40.