The American Journal of Surgery 221 (2021) 589–593

Contents lists available at ScienceDirect

The American Journal of Surgery

journal homepage: www.americanjournalofsurgery.com

Original Research Article

Duodenal complications in necrotizing pancreatitis: Challenges of an overlooked complication☆

Lucas R. Banter [a, *], Thomas K. Maatman [b], Sean P. McGuire [b], Eugene P. Ceppa [b], Michael G. House [b], Attila Nakeeb [b], Trang K. Nguyen [b], C. Max Schmidt [b], Nicholas J. Zyromski [b]

[a] Indiana University School of Medicine, Indianapolis, IN, USA
[b] Department of Surgery, Indiana University School of Medicine, Indianapolis, IN, USA

ARTICLE INFO

Article history:
Received 17 July 2020
Received in revised form
2 November 2020
Accepted 9 November 2020

Keywords:
Necrotizing pancreatitis
Duodenal fistula
Duodenal stricture
Acute pancreatitis

ABSTRACT

Background: Duodenal complications of necrotizing pancreatitis (NP) are challenging and understudied. We sought to characterize the demographics and clinical course of NP patients with duodenal complications.
Methods: Single institution retrospective review of 687 NP patients treated from 2005 to 2018.
Results: Duodenal complications developed in 40 (6%) patients including fistula in 11 (2%) and stricture in 29 (4%) patients. Patients with duodenal complications had increased computed tomography severity index (CTSI), degree of glandular necrosis, organ failure, infected necrosis, and disease duration. Mortality from NP was increased in patients with duodenal fistula (36%) compared to patients with duodenal stricture (7%) and patients without duodenal complications (9%). Surgical management of duodenal complications was required in 9/11 (82%) patients with fistula and 17/29 (59%) patients with stricture.
Conclusions: Duodenal complications occurred in 6% of necrotizing pancreatitis patients. Sixty five percent of patients with duodenal complications required surgical correction. Duodenal fistula was associated with increased mortality.

Background

Necrotizing pancreatitis (NP) is the most severe form of acute pancreatitis, carrying significant morbidity and mortality ranging from 10 to 30%.[1–3] NP is associated with a profound systemic and local inflammatory response that affects adjacent organs such as the colon, bile duct, and duodenum.[4] The central anatomic location of the pancreas in the abdomen places a host of adjacent organs at risk of complications from this local inflammation.

The duodenum is anatomically associated with the head of the pancreas. A variety of duodenal complications in NP have been reported in small series, including stricture and fistula.[5–7] Importantly, there has been a paradigm shift in the treatment of NP since the acceptance of the step-up approach for NP.[3] Since this shift, there has not been a systematic characterization of the type of duodenal complications observed in NP and the impact on clinical outcomes.

We therefore sought to characterize duodenal complications in a large series of NP patients. Specifically, we sought to identify risk factors for development, impact on patient outcomes, and patterns of treatment. We hypothesized that duodenal complications arising in necrotizing pancreatitis negatively impact morbidity and mortality.

Methods

Study population

All adult NP patients treated at a single institution (Indiana University Health University Hospital) between 2005 and 2018 were included in this study. Retrospective review of a prospectively maintained database identified patients with duodenal complications from NP, specifically duodenal fistula and stricture. Sociodemographic variables present at the time of disease onset

☆ †This work has been selected for oral presentation at the 2020 annual meeting of the Midwest Surgical Association.

* Corresponding author. Department of Surgery, Indiana University School of Medicine, 545 Barnhill Dr., Emerson Hall 519, Indianapolis, IN, 46202, USA.
E-mail address: nzyromsk@iupui.edu (L.R. Banter).

https://doi.org/10.1016/j.amjsurg.2020.11.022
0002-9610/

included age, sex, etiology of NP, and medical comorbidities. Variables evaluated during the NP clinical course included degree of pancreatic necrosis, computed tomography severity index (CTSI),[8] persistent organ failure, splanchnic vein thrombosis (SVT), infected necrosis, disconnected pancreatic duct syndrome (DPDS), necrosis intervention, readmission, disease duration, overall morbidity, and mortality. These variables were defined as described previously.[9] Patients who developed duodenal complications were compared to those who did not develop duodenal complications.

All patients with NP had long-term follow up in our necrotizing pancreatitis clinic with annual visits with a dedicated pancreatitis nurse coordinator.[10] This study was approved by the IU School of Medicine Institutional Review Board (IRB).

Statistical analysis

Data were analyzed with IBM® SPSS statistics 26.0 (IBM Corporation, Armonk, NY, USA). Categorical variables are described as number with frequency and compared using the chi-squared test. Continuous variables are described as mean with standard deviation (SD) or standard error of the mean (SEM) as indicated in table or figure legends and compared using independent samples Student's t-test. The strength of association between a risk factor identified in univariate analysis and duodenum complications was determined by calculating odds ratios (OR) with 95% confidence intervals (95% CI). *P* values less than 0.05 were accepted as statistically significant.

Results

Incidence and demographics

Among 687 patients treated for necrotizing pancreatitis from 2005 to 2018, 40 (6%) patients developed a duodenal complication; 11 (2%) patients developed a duodenal fistula and 29 (4%) patients developed a duodenal stricture. Most (29/40, 73%) were male. The average age was 53 ± 16 years. Pancreatitis etiology was most commonly biliary (n = 17, 43%). Demographic information, preexisting medical comorbidities, and pancreatitis etiology were similar between patients with and without duodenal complications (Table 1).

Clinical factors

Risk factors for duodenal complications are included in Table 1. Patients with duodenal complications had higher CTSI ($p = 0.049$) and more extensive pancreatic necrosis ($p = 0.003$) compared to patients without duodenal complications. The incidence of pancreatic head necrosis was similar between patients with and without duodenal complications ($p = 0.2$).

Organ failure was more common in patients with duodenal complications (Table 1). Respiratory failure was associated with a 2.5-fold (95% CI, 1.3–4.7; $p = 0.004$) increased risk and renal failure was associated with a 2.2-fold (95% CI, 1.1–4.3; $p = 0.02$) increased risk of duodenal complications. Cardiovascular failure was not associated with an increased risk of duodenal complications (OR, 1.8; 95% CI, 0.8–4.0; $p = 0.1$). Infected necrosis was diagnosed more frequently with duodenal complications: 85% of patients with duodenal complications had infected necrosis versus 51% of patients without duodenal complications ($p < 0.0001$).

Patients who developed duodenal complications were more likely to have undergone intervention for NP: 100% of patients with duodenal complications had either operative, endoscopic, or percutaneous intervention for their necrosis compared with 79% of patients without duodenal complications ($p = 0.001$). Patients with duodenal complications were more likely to have had more invasive intervention: 88% of patients underwent operative intervention compared to 63% of patients without duodenal complications ($p = 0.001$) (Table 1).

The presence of splanchnic vein thrombosis did not affect the development of duodenal complications. Isolated splenic vein thrombosis was diagnosed in 38% and portal vein and/or SMV thrombosis was diagnosed in 28% of patients with duodenal complications compared with 29% (splenic vein) and 20% (portal vein/SMV) of patients without duodenal complications (p = 0.3 and 0.3 respectively) (Fig. 1).

Therapy and outcomes

The median follow-up for the overall cohort was 23 months (IQR 7–60 months).

Diagnosis of duodenal fistula was established at an average of 92 ± 20 days from onset of NP whereas diagnosis of duodenal stricture was established at an average of 537 ± 138 days from NP onset. Duodenal stricture was diagnosed within a broad time range: the earliest stricture was diagnosed 23 days after NP diagnosis and the latest stricture was diagnosed 2482 days (6.8 years) from NP diagnosis. Two distinct times of duodenal stricture development were seen: 20 patients were diagnosed within the first two years after NP diagnosis while the remaining 6 were diagnosed three or more years after NP diagnosis (Fig. 2). The timing between NP diagnosis and stricture development was unable to be determined in three patients.

Thirty eight of forty (95%) patients with duodenal complications underwent surgical, endoscopic, or percutaneous intervention to treat duodenal pathology. Surgical management was required to correct duodenal complications in 26 (65%) patients while 12 (30%) patients were treated with endoscopic or percutaneous procedures alone.

Of patients who developed duodenal fistula, 82% underwent surgical intervention, 18% were treated endoscopically, and 73% required percutaneous intervention. 59% of patients who developed stricture underwent surgical intervention while 24% were treated endoscopically and none had percutaneous intervention (Table 2). Duodenal fistula patients required 4.5 ± 1 total interventions while stricture patients were managed with 1.0 ± 0.2 interventions. The average time from fistula to NP disease resolution 337 ± 134 days while time the time from duodenal stricture diagnosis to NP disease resolution was 61 ± 14 days. There was a wide range of surgical approaches to duodenal fistulae: three patients underwent duodenojejunostomy, two underwent duodenostomy, one underwent primary duodenal repair, and three were managed with wide drainage only (two of whom died prior to any further operative intervention). The remaining two patients were managed non-operatively. Endoscopic interventions included stenting and percutaneous interventions consisted of drain placement. In the duodenal stricture cohort, the majority of patients underwent gastrojejunostomy creation, though three patients underwent pancreatoduodenectomy. Endoscopic intervention included EGD and ERCP, either diagnostic or with dilation of the stricture.

Patients with duodenal complications had a significantly longer NP disease duration (10.6 ± 10.3 months) compared to patients without duodenal complications (6.3 ± 5.5 months), $p < 0.0001$. Both fistula and stricture patients were treated with total parenteral nutrition (TPN). Fistula patients required TPN for a longer duration (204 ± 63 versus 19 ± 5 days), $p < 0.0001$ (Table 2). Mortality rates were similar in patients with (15%) and patients without (9%) duodenal complications ($p = 0.2$) (Table 1). However, mortality rates of patients with duodenal fistula was 36% and

Table 1
Demographics and clinical outcomes in patients with and without duodenal complications.

	Duodenal Complication (n = 40)	Control (n = 647)	p
Demographics			
Male sex	29 (73%)	420 (65%)	0.3
Etiology			0.1
Biliary	17 (43%)	316 (49%)	
Alcohol	5 (13%)	138 (21%)	
Other	18 (45%)	193 (30%)	
Age[b]	53.1 ± 15.7 years	52.2 ± 15.6 years	0.7
Hypertension	25 (63%)	388 (60%)	0.8
Obesity	22 (55%)	324 (50%)	0.5
Tobacco Use	12 (30%)	270 (42%)	0.1
Diabetes Mellitus	10 (25%)	163 (25%)	1.0
Clinical Course			
[a]CT Severity Index[b]	7.3 ± 2.5	6.6 ± 2.0	0.049
Degree of Gland Necrosis			0.003
None	7 (18%)	91 (14%)	
<30%	8 (20%)	165 (26%)	
30–50%	6 (15%)	236 (36%)	
>50%	19 (48%)	155 (24%)	
Pancreatic Head Necrosis	21 (53%)	276 (43%)	0.2
[a]Organ Failure	23 (58%)	223 (34%)	0.003
[a]Respiratory	21 (53%)	199 (31%)	0.004
[a]Renal	15 (38%)	138 (21%)	0.02
Cardiovascular	9 (23%)	89 (14%)	0.1
Splanchnic Vein Thrombosis	22 (55%)	276 (43%)	0.2
[a]Infected Necrosis	34 (85%)	333 (51%)	<0.0001
[a]Necrosis intervention	40 (100%)	512 (79%)	0.001
[a]Intervention type			
None (medical)	0 (0%)	135 (21%)	0.001
PD only	1 (3%)	37 (6%)	
Endo only	1 (3%)	35 (5%)	
Minimally invasive combo	3 (8%)	33 (5%)	
OR only	13 (33%)	230 (36%)	
Combo Min invasive + OR	22 (55%)	177 (27%)	
[a]Disease Duration†	10.6 ± 10.3 months	6.3 ± 5.5 months	<0.0001
Mortality	6 (15%)	56 (9%)	0.2

Abbreviations: CT – computed tomography.
[a] Represents statistical significance with p < 0.05.
[b] Continuous variables reported as mean value with standard deviation.

patients with duodenal stricture was 7% ($p = 0.02$). Mortality in patients with duodenal fistula was also statistically higher than in patients that did not develop duodenal complications ($p = 0.002$) (Table 2).

A decision tree was developed to assist in management of NP-related duodenal complications (Fig. 3). For duodenal fistula, the decision tree emphasizes controlling sepsis first followed by a stepwise approach to treating duodenal fistula with percutaneous drains and endoscopic intervention prior to surgical intervention. For duodenal stricture, the decision tree emphasizes endoscopic intervention prior to surgery. Both decision trees highlight the importance of pursuing enteral nutrition: in general, we advocate for pursuing enteral nutrition either by mouth if possible or with enteric feeds beyond the level of the duodenal pathology. In cases where this is not possible, we opt to pursue TPN.

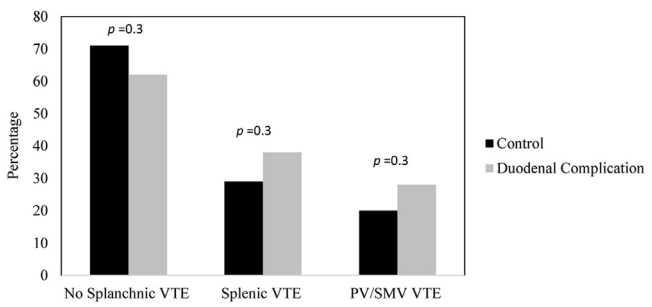

Fig. 1. Rates of splanchnic vein thrombosis among patients with and without duodenal complications.
*Patients with PV or SMV thrombosis in combination with splenic vein thrombosis were excluded from analysis; Abbreviations: PV- portal vein; SMV- superior mesenteric vein.

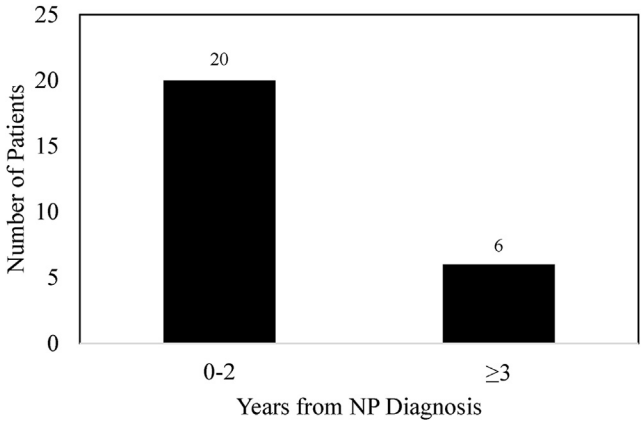

Fig. 2. Timing of duodenal stricture diagnosis from NP diagnosis; Abbreviations: NP-necrotizing pancreatitis.

Table 2
Diagnosis and management of duodenal fistula and duodenal stricture. Interventions reported are interventions related to duodenal pathology only. Continuous variables are reported as mean ± SEM.

	Duodenal Fistula (n = 11)	Duodenal Stricture (n = 29)	*p*
Time from NP onset to diagnosis (days) †	92 ± 20	537 ± 138	0.06
[a]Time from diagnosis to NP resolution (days) †	337 ± 134	55 ± 13	0.0002
Interventions (total)	4.5 ± 1	1.0 ± 0.2	<0.0001
Surgical			
(any)	9/11 (82%)	17/29 (59%)	0.77
[a](#)	1.7 ± 0.4	0.7 ± 0.1	0.01
Endoscopic			
(any)	2/11 (18%)	7/29 (24%)	0.68
(#)	0.2 ± 0.1	0.3 ± 0.1	0.46
Percutaneous			
[a](any)	8/11 (72%)	0/29 0%	<0.0001
[a](#)	2.2 ± 0.7	0 ± 0	<0.0001
[a]TPN (days)	204 ± 63	19 ± 5	<0.0001
[a]Mortality (%)	4/11 (36%)	2/29 (7%)	0.02

Abbreviations: NP- necrotizing pancreatitis; TPN- total parenteral nutrition.
[a] Represents statistical significance with $p < 0.05$.

Discussion

Duodenal complications are important but understudied sequelae of NP and consist of two separate entities: duodenal stricture and duodenal fistula, each of which have a distinct clinical course. We found an overall incidence of duodenal complications in NP of 6% (40/687); 2% (11/687) developed duodenal fistula and 4% (29/687) of patients developed duodenal stricture.

Among NP patients, risk factors for the development of duodenal complications included higher CTSI, increasing volume of gland necrosis, and respiratory and renal failure. Patients with duodenal complications have a prolonged disease course when compared with patients without duodenal complications. Furthermore, patients who developed duodenal fistula had a statistically significant increase in mortality compared with patients that developed stricture and with patients who did not develop duodenal complications. Duodenal complications were managed surgically in 65% of patients and endoscopically or percutaneously in the remaining 30% of patients.

Duodenal fistula and stricture are distinct clinical entities with vastly different impacts on NP disease course. Duodenal fistula develops earlier in the course of NP and extends the overall course of NP. Patients who develop duodenal fistula undergo an average of 4.5 additional procedures for duodenal fistula during the course of NP. Surgical management was varied amongst this cohort and multiple procedures were performed to manage fistula. This is in contrast to duodenal stricture in which all patients that required surgery underwent bypass.

This large series identified a relatively lower incidence of duodenal fistula compared with prior studies which ranged from 8 to 23%.[5–7] Within our study population, all patients who developed duodenal fistula had undergone operative, endoscopic, or percutaneous intervention for NP with the vast majority (88%) requiring operative intervention.

Duodenal stricture developed both early and late in the course of NP. This study provided a long term look at the course of NP with a median follow up of nearly two years. The finding that six patients developed stricture three or more years following initial diagnosis of NP suggests that the true incidence of duodenal stricture may be higher than previously appreciated. Duodenal stricture should be a consideration in NP patients presenting with feeding intolerance even years after initial diagnosis.

Surgical intervention for stricture among this population was common with 65% of patients eventually requiring surgical correction. Operative intervention included gastrojejunostomy and pancreatoduodenectomy. Strictureplasty has been used to treat duodenal stricture caused by Crohn's disease[11,12] and peptic ulcer disease related stricture.[13] In the setting of NP with very dense retroperitoneal inflammation, mobilization of the duodenum presents a specific technical challenge and explains the lack of strictureplasty attempted within this cohort.

This study has several limitations: this was a single-center study

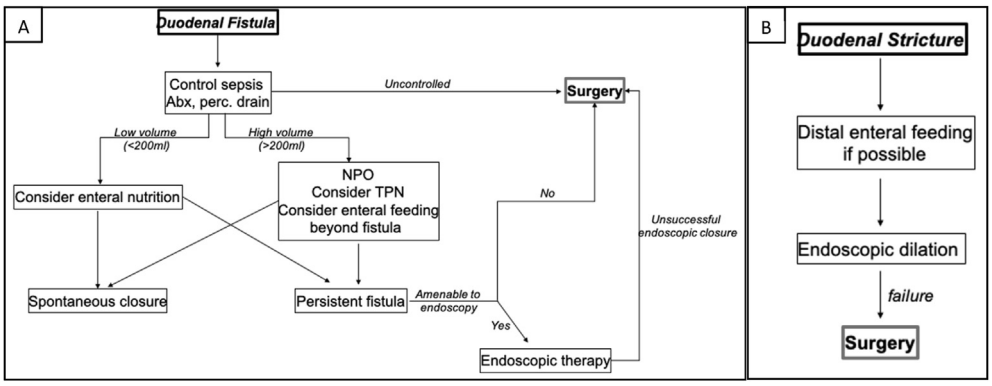

Fig. 3. Decision tree for management of duodenal fistula and stricture.; Abbreviations: Abx-antibiotics; perc drain-percutaneous drain into abdominal collection; NPO: nil per os; TPN- total parenteral nutrition.

conducted in a retrospective fashion, limiting insights into etiology. Duodenal fistula was diagnosed in two patients prior to any intervention, three patients after percutaneous drain placement, and four patients after operative debridement. The timing relative to procedures was unable to be determined in two patients. Fistula was present at the time of initial surgical debridement in multiple patients. This data suggests that the etiology of duodenal fistula is complex and likely multifactorial. However, we believe that the central etiology of most duodenal fistula is related to duodenal erosion from pancreatic necrosis. The mechanism underlying stricture is likely inflammation and scarring from the a combination of the pancreatic process itself extending to the duodenum as well as the need for multiple interventions throughout a prolonged disease course. Future work should focus on assessing if intervention—and which type—increases risk of duodenal complications.

Collectively, this large review of duodenal pathology in NP highlights the frequency of duodenal complications in NP. Duodenal complications develop in patients with organ failure, extensive and infected necrosis. There is a high rate of surgical intervention amongst patients with both duodenal fistula and duodenal stricture. Duodenal fistula is associated with increased mortality. Recognition of duodenal fistula should prompt due attention. Duodenal strictures may develop years after the initial NP insult, emphasizing the need for long term follow up of NP patients.

Author statement

LR Banter, TK Maatman, and SP McGuire were involved in acquisition, analysis, and interpretation of data in addition to drafting and revising the work. LR Banter, TK Maatman, SP McGuire, EP Ceppa, MG House, A Nakeeb, TK Nguyen, CM Schmidt, and NJ Zyromski were involved in the conception of the project, interpretation of the data, and revision of work. All authors were involved in the final approval. NJ Zyromski serves as the mentor and corresponding author and agrees to be accountable for the work.

Financial support

None.

Disclosures

None.

References

1. Petrov MS SS, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology*. 2010;139(3):813–820.
2. Maatman TK, Mahajan S, Roch AM, et al. High rates of readmission in necrotizing pancreatitis: natural history or opportunity for improvement? *J Gastrointest Surg*. 2019;23(9):1834–1839.
3. Van santvoort HC, Bakker OJ BM, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010;362(16):1491–1502.
4. Beger HG RB, Mayer J, Pralle U. Natural Course of Acute Pancreatitis. *World J. Surg*. 1997;21(2):130–135.
5. Doberneck RC. Intestinal fistula complicating necrotizing pancreatitis. *Am J Surg*. 1989;158(6):581–584.
6. Tsiotos GG SD. Sarr MG Incidence and Management of Pancreatic and enteric fistulas after surgical Management of severe necrotizing pancreatitis. *Arch Surg*. 1995;130(1):48–52.
7. Jiang W TZ, Yang D, Ke L, et al. Gastrointestinal fistulas in acute pancreatitis with infected pancreatic or peripancreatic necrosis: a 4-year single-center experience. *Medicine (Baltim)*. 2016;95(14):e3318.
8. Balthazar EJ RD, Megibow AJ, Ranson JH. *Acute Pancreatitis: Value of CT in Establishing Prognosis Radiology*. 174. 1990:331–336, 2.
9. Alexandra M, Roch TKM, Carr Rose A, Colgate Cameron L, et al. Zyromski venous Thromboembolism in necrotizing pancreatitis: an underappreciated risk. *J Gastrointest Surg*. 2019;23(12):2430–2438.
10. Maatman TK MK, Sood AJ, Ceppa EP, et al. Improved outpatient communication decreases unplanned readmission in necrotizing pancreatitis. *J Surg Res*. 2020;253:139–146.
11. Lightner AL FJ. Duodenal crohn's disease-a diagnostic conundrum. *J Gastrointest Surg*. 2018;22(4):761–763.
12. Yamamoto TBI, Connolly AB, Allan RN, Keighley MR. Outcome of strictureplasty for duodenal Crohn's disease. *Br J Surg*. 1999;86(2):259–262.
13. Maureen A, Chung HJW. *Surgical Management and Treatment of Gastric and Duodenal Fistulas Surgical Clinics of North America*. vol. 76. 1996:1137–1146, 5.