Perforation and fistula of the gastrointestinal tract in patients with necrotizing pancreatitis: a nationwide prospective cohort

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Perforation and Fistula of the Gastrointestinal Tract in Patients With Necrotizing Pancreatitis

A Nationwide Prospective Cohort

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Objective: The aim of this study was to explore the incidence, risk factors, clinical course and treatment of perforation and fistula of the gastrointestinal (GI) tract in a large unselected cohort of patients with necrotizing pancreatitis.

Background: Perforation and fistula of the GI tract may occur in necrotizing pancreatitis. Data from large unselected patient populations on the incidence, risk factors, clinical outcomes, and treatment are lacking.

Methods: We performed a post hoc analysis of a nationwide prospective database of 896 patients with necrotizing pancreatitis. GI tract perforation and fistula were defined as spontaneous or iatrogenic discontinuation of the GI wall. Multivariable logistic regression was used to explore risk factors and to adjust for confounders to explore associations of the GI tract perforation and fistula on the clinical course.

Results: A perforation or fistula of the GI tract was identified in 139 (16%) patients, located in the stomach in 23 (14%), duodenum in 56 (35%), jejunum or ileum in 18 (11%), and colon in 64 (40%). Risk factors were high C-reactive protein within 48 hours after admission [odds ratio (OR): 1.19; 95% confidence interval (CI): 1.01–1.39] and early organ failure (OR: 2.76; 95% CI: 1.78–4.29). Prior invasive intervention was a risk factor for developing a perforation or fistula of the lower GI tract (OR: 2.60; 95% CI: 1.04–6.60). While perforation or fistula of the upper GI tract appeared to be protective for persistent intensive care unit-admission (OR: 0.11, 95% CI: 0.02–0.44) and persistent organ failure (OR: 0.15; 95% CI: 0.02–0.58), perforation or fistula of the lower GI tract was associated with a higher rate of new onset organ failure (OR: 2.47; 95% CI: 1.23–4.84). When the stomach or duodenum was affected, treatment was mostly conservative (n = 54, 68%). Treatment was mostly surgical when the colon was affected (n = 38, 59%).

Conclusions: Perforation and fistula of the GI tract occurred in one out of six patients with necrotizing pancreatitis. Risk factors were high C-reactive protein within 48 hours and early organ failure. Prior intervention was identified as a risk factor for perforation or fistula of the lower GI tract. The clinical course was mostly affected by involvement of the lower GI tract.

Keywords: fistulas, gastrointestinal tract, necrotizing pancreatitis, perforations

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Acute pancreatitis is one of the most common gastrointestinal (GI) diseases causing hospital admission and has a rising incidence.[1] An important determinant for the severity of the disease is the development of necrosis of (peri-)pancreatic tissue, which occurs in 20% of patients.[2] Subsequently, infection of the

necrotic tissue occurs in one-third of patients with necrotizing pancreatitis.[3,4] A less common complication in patients with necrotizing pancreatitis is perforation or fistula of the GI tract. Perforation and fistula, defined as discontinuation of the GI wall either without or with connection with another organ, of the GI tract may involve the stomach, duodenum, jejunum, ileum, and colon.[5,6]

GI fistulas have a wide range in reported incidence, ranging from 3% to 67%.[1,6–11] Most of the GI fistulas are described within the upper GI tract (ie, stomach, duodenum), which often can be treated conservatively with a wait and see approach.[5,9] Perforation or fistula of the GI tract may severely impact patients' condition and lead to other complications, such as hemorrhage, deterioration of nutritional status, and sepsis,[9,11–13] especially when the colon is involved.[9,10,14–16] Despite potential benefits of nonsurgical approaches to colonic GI fistulas,[5,9,17–19] invasive surgical treatment is still recommended for colonic GI fistulas following acute necrotizing pancreatitis.[14,16,20]

Despite the fact that perforation and fistula of the GI tract are recognized in clinical practice, data on this topic are scarce, and consist mostly of small series of selected patients or case reports.[1,6–11] Subsequently, the magnitude of this entity remains unknown and guidelines on management are lacking. Therefore, these complications can often be missed, possibly leading to avoidable morbidity and mortality. This may be prevented by early detection and treatment by identifying high-risk patients early in the disease course. We therefore performed an observational study in a large unselected cohort of patients with necrotizing pancreatitis with the aim to explore the incidence, risk factors, clinical course and treatment of perforation and fistula of the GI tract.

METHODS

Study Design and Population

This was a post hoc long-term analysis of patients included in the nationwide prospective database (PWN CORE) of the Dutch Pancreatitis Study Group. A subset of these patients was included in previous randomized trials on invasive management of necrotizing pancreatitis.[3,21] All patients with acute pancreatitis in the nationwide registration cohort between November 2005 and December 31, 2015 were screened for eligibility. This time period was chosen to ensure follow-up of patients. For the current study, we included all adult patients with necrotizing pancreatitis, defined as a computed tomography severity index (CTSI) score of three or more. An expert radiologist (T.L.B.) reviewed all abdominal radiological images to determine the CTSI score, to assess the presence and location of peripancreatic collections and (peri)pancreatic necrosis, and to evaluate signs of perforation and fistula of the GI tract. Patients were excluded if they had signs of chronic pancreatitis according to the M-ANNHEIM criteria,[22] pancreatic carcinoma at admission, or a traumatic etiology of pancreatitis. For the current study, the need for ethical approval was waived by the medical ethics committee. It was conducted in accordance with the principles of the Declaration of Helsinki. This study was reported according to the "Strengthening the Reporting of Observational studies in Epidemiology" (STROBE) guideline.[23] All patients or their legal representatives gave written informed consent for registration. Treatment of acute pancreatitis was according to the international guidelines for management of acute pancreatitis.[18,19]

Patient Follow-up and Data Collection

Using a predefined, standardized case-record form, collection of data from medical records on multiple patient factors was performed. Clinical data were collected prospectively during the initial hospital admission and follow-up data were collected retrospectively. An additional data collection for long-term follow-up of all patients was performed in January 2020 to complete the data capture including data regarding perforation or fistula of the GI tract. If at any time before or during follow-up a patient was transferred to a different hospital, all the required follow-up data were retrieved from those institutions. All data were imported by one author (H.C.T.) in Open Clinica, a Good Clinical Practice-certified data management software, and subsequently verified by a second author (S.M.v.D). Discrepancies were resolved by consensus during research meetings of the Dutch Pancreatitis Study Group.

Study Outcomes and Definitions

All definitions were established after careful consideration of the current literature in research meetings of the Dutch Pancreatitis Study Group and are provided in the Supplementary Appendix Table S1, Supplemental Digital Content 1, http://links.lww.com/SLA/E75.

Perforation and fistula of the GI tract (stomach, duodenum, jejunum, ileum, or colon) confirmed with either imaging, endoscopy or surgery, were defined as a) perforation: a spontaneous or iatrogenic discontinuation of the gastrointestinal wall without a connection with another organ, or as b) fistula: spontaneous or iatrogenic discontinuation of the gastrointestinal wall with a connection with another organ (eg, pancreas or cutis (enterocutaneous fistula)). An enterocutaneous fistula was defined as a fistula, but could occur after a spontaneous or iatrogenic perforation. A subdivision was made in perforations or fistula of the upper (gastric and duodenum) and lower (jejunum, ileum, and colon) GI tract. When a perforation or fistula of the GI tract was only seen on imaging, images were reviewed by an expert radiologist (T.L.B.). Symptomatic perforation and fistula of the GI tract were defined as productive perforation and fistula by means of findings of GI content in external drain or hematemesis or melena. Asymptomatic perforation and fistula of the GI tract were defined as a radiological finding without GI content in external drain or hematemesis or melena. Intentional iatrogenic fistula as a result of endoscopic drainage were excluded from the definition of perforation or fistula of the GI tract due to the intentional nature. The cause of each perforation and fistula of the GI tract was defined as either spontaneous (ischemia/necrosis or diagnosis of a perforation or fistula with no prior invasive intervention), iatrogenic (confirmed iatrogenic cause by an inadvertent perforation during endoscopic intervention, percutaneous catheter drain or surgery) or unknown (no distinction between spontaneous or iatrogenic could be made, a combination could be possible). No distinction between perforation and fistula was made because it was in clinical practice not always possible to distinguish between the two entities.

Clinical course variables included pancreatitis-related mortality (death which occurred during admission for pancreatitis), total length of hospital stay, readmission and number of readmissions and (long-term) complications. Treatment and healthcare resources included pancreatic interventions, other interventions, intensive care unit (ICU) admission, length of ICU stay, single organ failure, multiple organ failure, and persistent organ failure during the entire follow-up. ICU stay and organ failure were classified as "early" or "delayed" ICU stay. Early was defined as within one week after admission and delayed was

defined as new or persistent organ failure after three weeks after admission. This cut-off value was deliberately chosen because it was not always possible to assess with full certainty when the perforation or fistula developed. A previous study has shown an onset of perforation and or fistula after four to eight weeks after onset of disease.[24] To be sure not to miss any previously developed perforation or fistula (based on the development of infected necrosis and subsequently pancreatic intervention) we have chosen a three-week cut-off value. Treatment of perforation or fistula of the GI tract consisted of conservative measurements, including patients with a percutaneous drain in situ at diagnosis, minimal invasive measurements, including percutaneous and endoscopic treatment strategies or invasive measurements, including surgery.

Statistical Analysis

Patients characteristics, incidence and clinical course were reported descriptively. Descriptive numerical data were reported as mean with SD when normally distributed and as median with interquartile ranges (IQR: P25–P75) when not normally distributed. Categorical data were shown as frequencies and percentages. A multivariable logistic regression model to determine risk factors for developing a perforation or fistula of the upper and lower GI tract was fitted when deemed possible, which was predefined as having more than 50 events of the outcome. The clinical course was compared for patients with and without perforation or fistula of the GI tract. Subgroup analyses were performed to compare clinical course of patients with and without symptomatic perforation or fistula of the GI tract. Statistical comparison was performed using the Fisher exact test or χ^2 test for categorical data and the Student t test or the Mann-Whitney U test for continuous data. Univariate analysis will be presented in the Supplementary Appendix S4, Supplemental Digital Content 1, http://links.lww.com/SLA/E75. Multivariable logistic regression models that adjusted for confounding to ascertain the independent effect of perforation or fistula of the GI tract were fitted for several clinical outcomes. The presence of perforation or fistula of the GI tract was used as a dependent variable. The variables included as covariates to adjust for potential confounding varied by clinical outcome and consisted

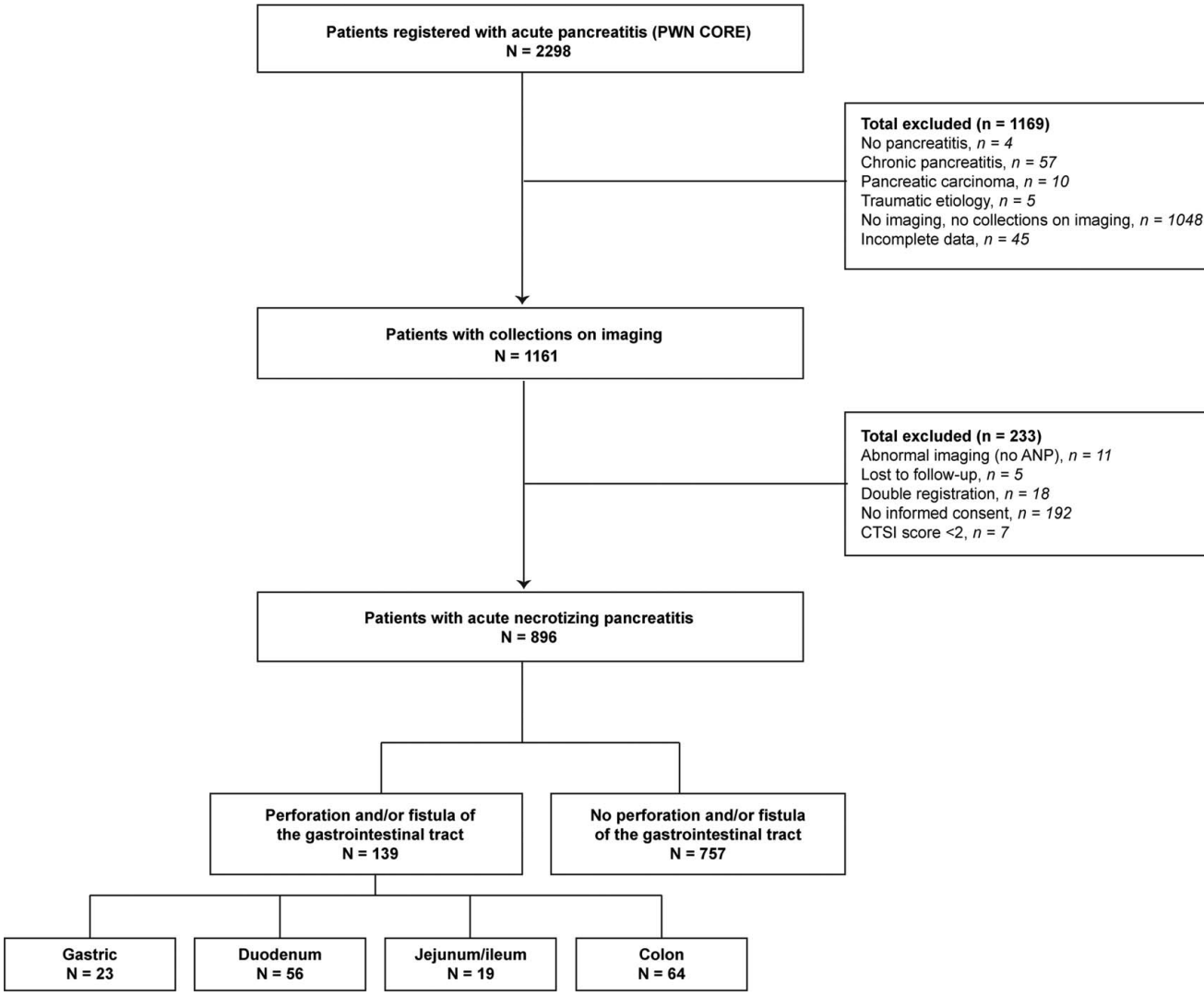

FIGURE 1. Inclusion flowchart.

of a combination of age, C-reactive protein, sex, American Society of Anesthesiologists (ASA) classification, presence of parenchymal necrosis, extent of necrosis, occurrence of infected necrosis or early onset of organ failure or abdominal compartment syndrome (ie, the last three all before diagnosis of a perforation or fistula of the GI tract). The variables included in the regression model are presented in the Supplementary Appendix Table S5, Supplemental Digital Content 1, http://links.lww.com/SLA/E75. If applicable, we calculated relative risk or adjusted odds ratios (OR) with their respective 95% confidence intervals (95% CI). Treatment strategies for perforation or fistula of the GI tract were reported descriptively for each location and subsequently for comparing with and without symptomatic perforation or fistula of the GI tract. A P value <0.05 was considered statistically significant. Statistical analysis was performed using (R version 4.1.2 (2021-11-01); R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between November 2005 and December 2015, 2289 patients with acute pancreatitis were registered in the nationwide prospective registry. A total of 896 patients met the study criteria for necrotizing pancreatitis and were included in the current study (Fig. 1). Median age of the patients at time of admission for the initial episode of acute pancreatitis was 58 (IQR: 47–69) years. Parenchymal necrosis with or without extrapancreatic necrosis occurred in 542 (60%) patients and 354 (40%) patients had extrapancreatic necrosis only. Infected necrosis occurred in 481 (54%) patients. A total of 468 (52%) patients underwent an invasive intervention for (peri-)pancreatic collections. Pancreatitis-related mortality from the initial admission until last follow-up date was 12%. Median follow-up was 75 (IQR: 41–151) months.

Perforation and Fistula of the GI Tract

Patients characteristics at admission and clinical disease course are provided in Table 1. Interventions and complications are summarized in the Supplementary Appendix Table S2, Supplemental Digital Content 1, http://links.lww.com/SLA/E75. A perforation or fistula of the GI tract occurred in 139 (16%) patients after a median of 52 (IQR: 28–85) days after admission. In 96 (69%) of these patients, an invasive intervention was performed before diagnosis of the GI perforation or fistula (baseline characteristics of patients with prior and no prior intervention are presented in the Supplementary Appendix Table S3, Supplemental Digital Content 1, http://links.lww.com/SLA/E75). There was a median of 31 (IQR: 12–60) days between the first intervention and diagnosis of the GI perforation or fistula and a median of 13 (4–27) days between the last intervention and diagnosis of the perforation or fistula. In the 139 patients who developed a perforation or fistula, a total of 162 perforations or fistulas were identified. The location was stomach in 23 (14%) patients, the duodenum in 56 (35%) patients, the jejunum or ileum in 19 (12%) patients and the colon in 64 (40%) patients.

Symptoms at presentation of perforation or fistula, etiology, and diagnostic modalities used are presented in Table 2. Most often the diagnosis of a perforation or fistula was an incidental finding (n = 91, 65%) and were asymptomatic. Forty-eight (35%) patients had a symptomatic perforation or fistula. Diagnosis of a perforation or fistula of the GI tract was achieved through finding fecal content in external drain fluid in 31 (22%) patients, oral administered methylene blue in external drain fluid in four (4%) patients, fistulography in 35 (25%) patients, gastroduodenoscopy in 30 (22%) patients, computed tomography in 47 (34%) patients, magnetic resonance imaging in two (1%) patients, surgery in 36 (26%) patients, and autopsy in seven (5%) patients (ie, multiple modalities may be used in patients).

Risk Factors

Independent risk factors for developing a perforation or fistula of the GI tract are presented in Table 3. High C-reactive protein within 48 hours after admission and organ failure within seven days after admission were associated with a perforation or fistula of the GI tract (adjusted OR: 1.26; 95% CI: 1.04–1.55 and adjusted OR: 2.24; 95% CI: 1.30–3.86, respectively). Intervention prior to the diagnosis of a GI perforation or fistula was found to be associated with the development of perforation or fistula of the lower GI tract (adjusted OR: 2.60; 95% CI: 1.04–6.60).

Clinical Course

Multivariate analysis on the clinical course is presented in Table 4. Of the 139 patients with a perforation or fistula of the GI tract, 49 (36%) patients were admitted in the ICU at time of diagnosis of the perforation or fistula of the GI tract. After diagnosis, new admission to the ICU occurred in 28 (21%) patients. Organ failure was present in 46 (34%) patients at time of diagnosis, new organ failure after diagnosis occurred in 22 (17%). Pancreatitis-related mortality did occur more often in patients with a perforation or fistula of the GI tract ($P < 0.01$), but an independent association was not found (adjusted OR: 1.25; 95% CI: 0.66–2.29). The presence of a perforation or fistula of the upper GI tract was associated with less persistent ICU admission for more than three weeks after admission (adjusted OR: 0.11; 95% CI: 0.02–0.44) and less persistent organ failure after three weeks after admission (adjusted OR: 0.15; 95% CI: 0.02–0.58). Associations were also found between a perforation or fistula of the lower GI tract and new onset organ failure after three weeks after admission (adjusted OR: 2.47; 95% CI: 1.23–4.84). Symptomatic perforation or fistula of the GI tract was not associated with a worse clinical outcome.

Treatment of Perforation or Fistula

Details on treatment of patients with a perforation or fistula of the GI tract are provided in Table 5. No differences in treatment strategy or number of deaths were found for patients with or without symptoms (Supplementary Appendix Table S6, Supplemental Digital Content 1, http://links.lww.com/SLA/E75).

Gastric perforation or fistula (n = 23) was treated conservatively without any invasive intervention in 15 (65%) patients, of whom six (40%) patients already had a percutaneous catheter drain in situ. Drainage of the perforation or fistula was performed in five (22%) patients, with percutaneous drainage in one (20%) and endoscopic drainage through dilatation of the perforation or fistula in four (36%) patients. In three (13%) patients, an attempt was made to close the perforation or fistula, all by means of suturing the defect: one (33%) patient required a relaparotomy with drainage of the abscess and one (33%) patient died.

Perforation or fistula of the duodenum (n = 56) was treated conservatively without any invasive intervention in 39 (70%) patients, of whom 27 (69%) patients already had a percutaneous catheter drain in situ. In 14 (25%) drainage of the perforation or fistula was performed: percutaneous drainage in six (43%) patients and endoscopic drainage through dilatation of the perforation or fistula in eight (57%) patients. In three (5%) patients, an attempt was made to close the perforation or fistula surgically, one patient (33%) required multiple surgical

TABLE 1. Patients Characteristics at Admission and Clinical Course* of Patients With Necrotizing Pancreatitis

		Perforation or Fistula of the Gastrointestinal Tract		
	Overall, N = 896	**No, N = 757**	**Yes, N = 139**	***P***
Age (y)	58 (47–69)	58 (46–69)	59 (50–70)	0.13
Male sex	571 (64)	473 (62)	98 (71)	0.08
Body mass index (kg/m^2)	27.1 (25–30.7)[a]	26.9 (25–30.7)[i]	27.8 (25.1–30.4)[j]	0.63
Etiology of pancreatitis				
Biliary	432 (48)	373 (49)	59 (42)	0.14
Alcohol	159 (17)	133 (18)	26 (19)	0.72
ASA				
I	298 (33)	255 (34)	43 (31)	0.56
II	471 (53)	390 (52)	81 (58)	0.17
III	123 (14)	108 (14)	15 (11)	0.35
IV	4 (0.4)	4 (1)	0	1.00
Severity of disease				
Leukocytes (10^9/l)	18.2 (14.4–22.2)[b]	18 (14.3–22.1)[j]	18.6 (14.9–22.9)[m]	0.25
C-reactive protein (mg/l)	297 (216–377)[c]	293 (208–368)[k]	341 (254–412)[n]	< 0.01
CT severity index	6 (4–8)[d]	6 (4–8)[l]	6 (5–10)	< 0.01
Parenchymal necrosis[e]	542 (60)	437 (58)	105 (76)	< 0.01
< 30	259 (48)	219 (50)	40 (38)	1.00
30–50	132 (24)	112 (26)	20 (19)	1.00
> 50	150 (28)	105 (24)	45 (43)	< 0.01
Pattern parenchymal necrosis[e]				
Right	15 (3)	11 (3)	4 (4)	0.27
Left	52 (10)	47 (11)	5 (5)	0.32
Central	233 (43)	181 (41)	52 (50)	< 0.01
Subtotal	76 (14)	52 (12)	24 (23)	< 0.01
Diffuse	161 (30)	141 (32)	20 (19)	0.28
Extrapancreatic necrosis only	354 (40)	320 (42)	34 (25)	< 0.01
Early ICU admission†	309 (35)[f]	221 (29)	88 (63)[f]	< 0.01
Early organ failure‡	223 (25)[g]	157 (21)[g]	66 (47)	< 0.01
Persistent single organ failure	61 (7)[h]	52 (7)[h]	9 (6)	1.00
Persistent multiple organ failure	137 (15)[h]	85 (11)[h]	52 (37)	< 0.01
Death pancreatitis related§	106 (12)	78 (10)	28 (20)	< 0.01

Data are presented as n (%) or median (interquartile range: P25–P75).
*Clinical course variables are reported regardless of timing of diagnosis of perforation or fistula of gastrointestinal tract.
†ICU admission within 21 days after admission.
‡Organ failure within seven days after admission.
§Death pancreatitis related is defined as death during admission or readmission for acute pancreatitis or complications due to acute pancreatitis.
Missing patients: a = 494, b = 82, c = 125, d = 8, e = pattern and extent necrosis missing in 1 patient, f = 6, g = 4, h = 5, i = 428, j = 66, k = 105, l = 1, m = 16, n = 20.
ASA indicates American Society of Anesthesiologists, assessed based on the patient's history just prior to admission, there were no patients with ASA class 5; CT, computed tomography; ICU, intensive care unit..

procedures and eventually underwent duodenal reconstruction. One (33%) patient died after the surgical attempt to close the perforation or fistula.

Jejunum or ileum perforation or fistula (n = 19) was treated conservatively without any invasive intervention in 10 (65%) patients, of whom seven (70%) patients had a percutaneous catheter drain in situ. Drainage was performed in three (17%) patients, by means of percutaneous catheter drainage in one (33%) patient and endoscopic drainage or dilatation of the fistula or perforation in two (67%) patients. In six (33%) patients, an attempt was made to close the perforation or fistula, endoscopically in one (17%) patient and surgically in five (83%) patients. One (17%) patient died after surgical treatment and one (17%) patient required relaparotomy with drainage after and eventually an ileostomy after the initial attempt to close the perforation surgically.

Colon perforation or fistula (n = 64) was treated conservatively without any invasive intervention in 22 (34%) patients, of whom 11 (50%) patients had a percutaneous catheter drain in situ. Drainage of the perforation or fistula was performed in four (6%) patients, all with percutaneous drainage. In 38 (59%) patients, an attempt was made to close the perforation or fistula surgically (suturing the defect n = 4, ileostomy n = 30, both sutures and ileostomy n = 4). Nine (24%) patients died after the surgical procedure, 10 (26%) patients required additional intervention (total parenteral nutrition due to persistent fistula n = 1, relaparotomy with drainage of abscess n = 5 and relaparotomy with ileostomy n = 3).

DISCUSSION

Although perforation and fistula of the GI tract are well recognized as a severe complication of acute pancreatitis, high quality data to guide clinical decision making are largely lacking. This large nationwide cohort study reveals a 16% incidence of a perforation or fistula of the GI tract in patients with necrotizing pancreatitis, and an incidence of 25% in patients with infected necrosis. High C-reactive protein, and early organ failure were identified as independent risk factors. A prior invasive intervention was identified as a risk factor for a perforation or fistula of the lower GI tract. We show that the clinical course of patients with necrotizing pancreatitis is apparently negatively impacted by a perforation or fistula of the lower GI tract, while a perforation or fistula of the upper GI tract appeared to be protective. Perforation or fistula of the upper GI tract closed spontaneously

TABLE 2. Clinical Presentation and Used Diagnostic Modalities

	Location of Perforation or Fistula of the Gastrointestinal Tract			
	Stomach, N = 23	Duodenum, N = 56	Jejunum/Ileum, N = 19	Colon, N = 64
Clinical symptoms				
Asymptomatic	16 (52)	38 (68)	11 (58)	38 (59)
Symptomatic	7 (30)	18 (32)	8 (42)	26 (41)
Hematemesis/melena	3 (13)	6 (11)	2 (11)	3 (5)
Signs of gastrointestinal content in external drain fluid	4 (17)	12 (21)	6 (32)	23 (36)
Intervention before diagnosis	14 (61)*	35 (63)†	12 (63)‡	46 (72)§
Diagnostic modality§				
Gastrointestinal content in external drain fluid	4 (17)	8 (14)	6 (33)	22 (34)
Methylene blue in external drain fluid	0	2 (4)	1 (6)	1 (2)
Fistulography	3 (13)	17 (30)	7 (39)	13 (20)
Endoscopy	8 (35)	20 (36)	2 (11)	3 (5)
CT	9 (39)	17 (30)	3 (17)	27 (42)
MRI	2 (4)	0	0	0
Surgical	2 (9)	9 (16)	7 (39)	30 (47)
Autopsy	1 (4)	2 (4)	2 (11)	5 (8)

Data are presented as n (%).

*Type of first intervention: percutaneous catheter drain n = 8, endoscopic transluminal drain n = 3, ascites drain n = 1, laparotomy n = 2. Type of last intervention: percutaneous catheter drainage n = 9, endoscopic transluminal drain n = 2, laparotomy n = 3.

†Type of first intervention: percutaneous catheter drain n = 24, endoscopic transluminal drain n = 3, ascites drain n = 5, laparotomy n = 3. Type of last intervention: percutaneous catheter drainage n = 22, endoscopic transluminal drain n = 1, ascites drain n = 2, laparotomy n = 3, minimal invasive surgery or VARD n = 6, PTC drain n = 1.

‡Type of first intervention: percutaneous catheter drain n = 6, endoscopic transluminal drain n = 1, ascites drain n = 1, laparotomy n = 2, minimal invasive surgery or VARD n = 1. Type of last intervention: percutaneous catheter drainage n = 5, endoscopic transluminal drain n = 1, laparotomy n = 2, minimal invasive surgery or VARD n = 3.

§Type of first intervention: percutaneous catheter drain n = 20, endoscopic transluminal drain n = 3, ascites drain n = 10, laparotomy n = 10, minimal invasive surgery or VARD n = 2. Type of last intervention: percutaneous catheter drainage n = 28, ascites drain n = 1, laparotomy n = 8, minimal invasive surgery or VARD n = 6, endoscopic transluminal necrosectomy n = 1.

CT indicates computed tomography; MRI, magnetic resonance imaging; PTC, percutaneous transhepatic cholangiography; VARD, video-assisted retroperitoneal debridement.

in the majority of the patients, while colon perforation and fistula were predominantly treated surgically.

There is wide variation in the reported incidence (3%–67%) of perforation or fistula of the GI tract.[1,6–11] This could be explained by the different study populations (eg, cohort consisting of patients with infected necrosis only) and limited number of patients included in previously published studies. The incidence found in the present study is in line with two recent studies,[8,9] but slightly higher than reported in other studies,[1,7,10] which could be due to the fact that we included only patients with necrotizing pancreatitis. In addition, our study has a high incidence of infected necrosis, which is explained by the fact that we have included patients from the intervention studies PANTER and TENSION.[3,21]

Failure of the intestinal barrier is thought to be associated with severe local inflammatory response, which may, especially when infected necrosis occurs, erode blood vessels directly, enhance thrombosis and reduce capillary perfusion.[25] In addition, inflammation and exposure to pancreatic enzymes can also lead to vascular thrombosis and worsening of the condition of the GI tract leading to the formation of edema, thrombosis, ischemia and necrosis.[6,11,26] Eventually this may cause

TABLE 3. Risk Factors for Developing a Perforation or Fistula of the Gastrointestinal Tract

	Perforation or Fistula of the Gastrointestinal Tract					
	Overall (N = 139)		Upper GI tract (N = 78)		Lower GI tract (N = 74)	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (y)	1.01 (1.00–1.03)	0.07	1.02 (1.00–1.03)	0.12	1.00 (0.98–1.02)	0.82
Male sex	1.33 (0.85–2.12)	0.22				
ASA 3+4	0.55 (0.28–1.04)	0.08				
CRP (mg/l)	**1.19 (1.01–1.39)**	**0.04**	1.26 (1.04–1.55)	**0.02**	1.06 (0.87–1.29)	0.59
Right necrosis	2.76 (0.56–10.54)	0.16				
Left necrosis	0.58 (0.13–1.84)	0.41				
Central necrosis	1.54 (0.79–2.96)	0.20				
Subtotal necrosis	1.16 (0.42–3.16)	0.78				
Necrosis 30%–50%	0.73 (0.35–1.52)	0.41				
Necrosis > 50%	1.70 (0.77–3.77)	0.19	2.27 (1.24–4.08)	**0.01**	1.49 (0.79–2.74)	0.20
Infected necrosis*	1.81 (0.92–3.56)	0.09	**3.44 (1.52–7.81)**	**< 0.01**	1.02 (0.43–2.53)	0.96
Early organ failure	**2.76 (1.78–4.29)**	**< 0.01**	**2.24 (1.30–3.86)**	**< 0.01**	2.13 (1.21–3.72)	**0.01**
Prior intervention†	1.03 (0.52–2.07)	0.92	0.49 (0.22–1.09)	0.07	2.60 (1.04–6.60)	**0.04**

*Before diagnosis perforation or fistula of the gastrointestinal tract, or overall in case of no occurrence of perforation or fistula of the gastrointestinal tract.

†Before diagnosis perforation or fistula of the gastrointestinal tract, or overall in case of no occurrence of perforation or fistula of the gastrointestinal tract.

ASA indicates American Society of Anesthesiologists; CRP c-reactive protein.

TABLE 4. Clinical Course in Patients With Perforation or Fistula of the Gastrointestinal Tract and the Different Locations*

	Upper GI Tract, n (%)		Lower GI Tract, n (%)	
	No, N = 818	Yes, N = 78	No, N = 822	Yes, N = 74
Death				
All pancreatitis related	93 (11)	13 (17)	86 (10)	20 (27)
OR (95% CI); *P*	0.67 (0.29–1.44); 0.32		1.49 (0.71–3.06); 0.28	
After 21 d after admission	74 (9)	11 (15)	69 (9)	16 (23)
OR (95% CI); *P*	1.02 (0.40–2.37); 0.97		0.94 (0.38–2.19); 0.90	
ICU admission				
New after 21 d after admission	174 (19)[a]	24 (32)[e]	141 (18)[b]	30 (43)[i]
OR (95% CI); *P*	0.58 (0.27–1.15); 0.13		1.41 (0.71–2.72); 0.31	
Persistent admission after 21 d after admission	124 (16)[b]	26 (34)[e]	116 (15)[h]	34 (49)[f]
OR (95% CI); *P*	0.11 (0.02–0.44); 0.01		2.71 (0.87–7.89); 0.07	
Organ failure				
New after 21 d after admission	126 (16)[c]	23 (31)[f]	123 (15)[b]	26 (38)[g]
OR (95% CI); *P*	0.48 (0.20–1.03); 0.07		2.47 (1.23–4.84); 0.01	
Persistent organ failure 21 d after admission	101 (13)[d]	16 (22)[g]	87 (11)[d]	30 (44)[g]
OR (95% CI); *P*	0.15 (0.02–0.58); 0.02		1.51 (0.43–4.88); 0.50	

*Binomial regression (binary data).

Patients who died (n = 21) within 21 d after admission were excluded for this analysis, this included 5 patients with a diagnosis of perforation or fistula of the gastrointestinal tract within 21 d after admission. Data was not imputed. Missing patients: a = 27, b = 24, c = 26, d = 35, e = 2, f = 4, g = 6, h = 22.

perforation and the formation of a fistula of the GI tract.[11] In addition, a perforation or fistula can also be iatrogenic through puncture of the GI wall or through erosion of the drain against the——already vulnerable—GI wall. Since there is no standardized diagnostic work-up to evaluate for potential perforations or fistulas of the GI tract before the patient undergoes an intervention, it is difficult to determine whether the perforation of fistula was already present. The run-up to the development of a iatrogenic or spontaneous perforation or fistula is different, the outcome, however, remains the same: either a perforation or fistula of the GI tract. Furthermore, there might be a difference in clinical course between acute perforations and chronic fistula formation.

The colon is more prone to ischemia as a result of low-flow state or the hemodynamic response to sepsis, as compared with the stomach and the jejunum and ileum due to the better blood supply of these organs.[11,12,20] More specifically, the transverse colon and the splenic flexure of the colon are closely related to the pancreas and inflammation of the body and tail may cause extrinsic impression and are therefore the most common sites involved.[26] Inflammation of the body of the pancreas as a factor for developing a complication of the colon could explain the finding that central necrosis is an independent risk factor for developing a colon perforation or fistula. Prior intervention was found to be a significant risk factor for developing a fistula or perforation of the lower GI tract, but was not found to be

TABLE 5. Treatment Strategies for the Different Locations of Perforation or Fistula of the Gastrointestinal Tract With and Without Symptoms

	Gastric, N = 23, n (%)	Duodenum, N = 56, n (%)	Jejunum/Ileum, N = 19, n (%)	Colon, N = 64, n (%)
Death without specific treatment	2 (9)	8 (14)	3 (16)	7 (11)
Conservative*	15 (65)	39 (70)	10 (56)	22 (34)
Percutaneous catheter drainage in situ	6 (40)	27 (69)	7 (70)	11 (50)
Drainage of perforation or fistula	5 (22)	14 (25)	3 (17)	4 (6)
Percutaneous (new drain)	1 (20)	6 (43)[b]	1 (33)[d]	4 (100)[f]
Endoscopic	4 (80)[†]	8 (57)	2 (67)	0
Dilatation of the fistula or perforation	4 (100)	8 (14)	1 (50)	0
Closure of perforation or fistula	3 (13)	3 (5)	6 (33)	38 (59)
Endoscopic	0	0	1 (17)	0
Endoscopic clips	0	0	1 (50)	0
Surgical	3 (100)[a]	3 (100)[c]	5 (83)[e]	38 (100)[g]
Sutures	3 (100)	1 (33)	2 (40)	4 (11)
Stoma	0	0	3 (60)[h]	30 (79)[i]
Both sutures and ileostomy	0	0	0	4 (11)[i]
Other	0	2 (67)[‡]	0	0

Data are presented as n (%).

*Conservative treatment includes no action to let the perforation or fistula heal spontaneousloy, medical therapy or leaving the perforation or fistula heal with a percutaneous catheter drain already in situ.

† = in 1 (8%) patient this was in addition to the percutaneous drain already in place.

‡ = in one patients decompression laparotomy with percutaneous catheter drainage and in one patient a new percutaneous catheter drain and a percutaneous transhepatic cholangiography drain and reconstruction of the duodenum by a gastro- and jejunostomy with a side-to-side Roux-en-Y.

[a]One patient died after surgical closure of perforation or fistula. [b]Two patients died after a new percutaneous drain. [c]One patient died after surgical treatment. [d]One patient died after placement of a new percutaneous catheter drain. [e]One patient died after surgical treatment. [f]One patient died after an additional percutaneous catheter drain. [g]Nine patients died after surgical treatment. [h]One (33%) patient had a stoma reversal, in two (67%) patients the stoma was permanent. [i]Twenty-one (62%) patients had a stoma reversal, in 13 (38%) patients the stoma was permanent.

significant in developing overall or upper GI perforations or fistulas. This might be explained by the lower GI tract, especially the colon, being more exposed and vulnerable due to inflammation and intervention. A previous study reported diagnosis of a GI fistula four to eight weeks after onset of pancreatitis in the majority of the patients.[24] This is in line with our findings (ie, a median of 52 d). These results confirm the suggestion that the occurrence of a perforation or fistula of the GI tract is associated with a prolonged exposure to the peripancreatic or pancreatic inflammation and necrosis or to prolonged percutaneous catheter drainage, which starts with inflammation and ends with perforation or obstruction. Therefore, timely drainage of infected necrosis could potentially decrease the risk of perforation or fistula of the GI tract. However, intervention may also play a role in the development of a perforation or fistula and therefore the risks should be considered. The recent published POINTER trial did, however, not show superiority of immediate catheter drainage (< 24 h after diagnosis of infected pancreatic necrosis), as compared with a delayed catheter drainage strategy. A postponed catheter drainage required less interventions for infected pancreatic necrosis and eventually over one-third patients did not require any intervention at all.[27] Therefore, identifying the patients at higher risk for developing a perforation or fistula of the GI tract is important. Potential risk factors for developing a perforation or fistula of the GI tract were evaluated. High C-reactive protein and early organ failure were found to be independent risk factors. One other previous study also showed that infected necrosis was found to be a risk factor for developing a perforation or fistula of the GI tract.[8] This previous study also showed early enteral nutrition to be a protective factor. This could have been influenced by bias (ie, patients not tolerating enteral nutrition may have been more critically ill) or it might be explained by preservation of the gut mucosal integrity, inhibition of bacterial overgrowth and translocation and reduction of the systemic inflammation and risk of infected necrosis.[28–30] With regards to colonic perforation, the presence of at least two collections in different locations seemed to be a significant risk factor.[31,32] Unfortunately, both data regarding early nutrition and the number and location of collection were not available for our study.

Surgical or radiological interventions, especially open necrosectomy, may also be a direct cause of perforation or fistula of the GI tract.[15,20,21,33] The management of infected necrosis has changed over the years from open to minimally invasive techniques used in a step-up approach.[21] In the present study, patients from the period before and after the implementation of the step-up approach were included. Overall, 68% of the patients underwent an invasive intervention before diagnosis of a perforation or fistula of the GI tract. This supports the notion that surgical intervention may increase the risk of GI complications. A previous smaller study from our group, however, suggested that the method of invasive management did not affect the incidence of GI fistula.[21] Furthermore, another smaller trial also observed no difference in occurrence of perforation of a visceral organ or enterocutaneous fistula requiring intervention between patients who underwent endoscopic step-up approach and surgical step-up approach (8% vs. 17%).[3] Unfortunately, minimally invasive therapy cannot be seen as the solution to prevent perforation or fistula of the GI tract in patients with infected necrotizing pancreatitis.

Perforation or fistula of the GI tract is associated with increased morbidity due to subsequent complications such as hemorrhage and sepsis.[5,7] In our study, the presence of a perforation or fistula of the GI tract was associated with a more severe clinical course with a higher rate of ICU admissions and organ failure. These results are in line with a single-center study.[9] They also found an increased mortality in patients with a fistula of the colon,[9] this could not be confirmed with the results of our study. It is hypothesized that spontaneous passage of the peripancreatic of pancreatic necrosis into the GI tract could improve the clinical status of the patient with resolution of pressure symptoms, by creating a natural drainage route.[5,34] This is similar to the route created when an endoscopic drainage is performed. This could explain the less severe disease course in patients with a gastric or duodenal complication, in whom a spontaneous cause was most often found. In the present study, mortality was not found to be significantly higher in patients with a GI complication compared with those without, which was also reported in previous studies.[5,11]

In the current study, perforation or fistula of the stomach, duodenum, jejunum, and ileum could most often be treated conservatively, either with or without percutaneous drains already in situ. Perforations or fistulas of the colon were most often treated surgically. As reported in previous studies, the location of the perforation or fistula may determine the treatment strategy, with spontaneous resolution in the majority of the complications of the upper GI tract while a perforation or fistula of the colon require surgical intervention in the majority.[5,11,14,16,20,35] There are, however, some reports showing potential benefits from conservative or less invasive measurements, such as percutaneous catheter drainage or endoscopic therapy, for patients with a perforation or fistula of the colon.[17–20] In our study, a total of 29% of the patients with a colon perforation or fistula could be successfully treated without invasive intervention or with less invasive techniques, such as percutaneous catheter drainage or endoscopic therapy. Due to the increase in experience in the field of endoscopy, this number could be even higher in current clinical practice. Due to the complexity and accessibility of the colon perforation or fistula and the potential fecal contamination during the procedure, however, endoscopic or other less invasive interventions may be difficult. Since we had no prospective treatment protocol when a perforation or fistula occurred, it was decided by the treating clinician which treatment was applied, according to local preference and experience. In addition to the current idea that colon perforations or fistulas still need to be treated surgically, this will generally also have been the first choice. Potentially, more of these patients could have been treated without invasive intervention, depending on the patients' clinical condition. In our study, we have shown the magnitude of the problem and the clinical consequences, which have not been reported in this manner before. Since the variation in location of the perforation or fistula is large, we cannot recommend specific treatment strategies with the current data. A more proactive diagnostic approach is, however, probably worthwhile. As for treatment, a tailored step-up approach, starting with conservative measures followed by minimally invasive measurements and eventually surgical treatment in absence of clinical improvement, could be considered for these patients. Future prospective studies are needed to define these approaches.

In conclusion, perforation or fistula of the GI tract occur in almost one out of six patients with necrotizing pancreatitis. The colon and duodenum are mostly commonly affected. C-reactive protein, early organ failure and abdominal compartment syndrome were identified as independent risk factors. The incidence rose to one in four patients with infected necrosis. Perforation or fistula of the GI tract are independently associated with a worse clinical course, especially for patients in whom the colon was affected. Perforation or fistula of the upper GI tract closed spontaneously in the majority of the patients, while colon perforation or fistula were predominantly treated surgically. Early

recognition and optimal treatment of perforation or fistula of the GI tract may improve the clinical outcomes and thereby quality of life of patients with necrotizing pancreatitis.

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