

# Gastrointestinal Fistulas in Acute Pancreatitis With Infected Pancreatic or Peripancreatic Necrosis

## A 4-Year Single-Center Experience

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**Abstract:** Gastrointestinal (GI) fistula is a well-recognized complication of acute pancreatitis (AP). However, it has been reported in limited literature. This study aimed to evaluate the incidence and outcome of GI fistulas in AP patients complicated with infected pancreatic or peripancreatic necrosis (IPN).

Between 2010 and 2013 AP patients with IPN who diagnosed with GI fistula in our center were analyzed in this retrospective study. And we also conducted a comparison between patients with and without GI fistula regarding the baseline characteristics and outcomes.

Over 4 years, a total of 928 AP patients were admitted into our center, of whom 119 patients with IPN were diagnosed with GI fistula and they developed 160 GI fistulas in total. Colonic fistula found in 72 patients was the most common form of GI fistula followed with duodenal fistula. All duodenal fistulas were managed by nonsurgical management. Ileostomy or colostomy was performed for 44 (61.1%) of 72 colonic fistulas. Twenty-one (29.2%) colonic fistulas were successfully treated by percutaneous drainage or continuous negative pressure irrigation. Mortality of patients with GI fistula did not differ significantly from those without GI fistula (28.6% vs 21.9%,  $P=0.22$ ). However, a significantly higher mortality (34.7%) was observed in those with colonic fistula.

GI fistula is a common finding in patients of AP with IPN. Most of these fistulas can be successfully managed with different procedures depending on their sites of origin. Colonic fistula is related with higher mortality than those without GI fistula.

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**Abbreviations:** AP = acute pancreatitis, CNPI = continuous negative pressure irrigation, CT = computed tomography, GI = gastrointestinal, ICU = intensive care unit, IPN = infected pancreatic or peripancreatic necrosis, MODS = the multiple organ dysfunction score.

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## INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with variable severity. It can be severe and associated with systemic or local complications, especially those with infected pancreatic or peripancreatic necrosis (IPN).<sup>1</sup> Gastrointestinal (GI) fistula is one of the well-recognized complications secondary to severe AP.<sup>2,3</sup> Depending on the sites of fistula, it may involve the stomach, duodenum, jejunum, ileum, and colon, either in combination or separately. It may result from direct erosion from digestive enzymes released by the inflamed pancreas on adjacent GI tract, or it could occur as a consequence of the intestinal necrosis due to vascular thrombosis in an area of inflammation and infection.<sup>4</sup> Additionally, GI fistulas may be associated with surgical intervention.<sup>5</sup> Although previous studies suggest the fistula of GI tract occurs infrequently in AP patients, IPN and the operative managements for IPN would increase the frequency. It has been reported GI fistulas may cause serious clinical consequences such as hemorrhage and exacerbation of infection with fatal outcome.<sup>2,5-7</sup> In this retrospective study we aimed to evaluate the incidence and clinical outcome of GI fistulas in the setting of AP with IPN.

## MATERIALS AND METHODS

Clinical data from patients with GI fistula secondary to AP between January 1, 2010 and December 31, 2013 in our center were retrospectively reviewed. Patients with chronic pancreatitis, known malignancy were excluded. The study center was a tertiary referral center at Jinling Hospital, Nanjing. The study was approved by the local research ethics committee.

AP was diagnosed according to clinical presentation (typically abdominal pain), laboratory parameters (serum amylase or lipase levels exceeding 3 times the upper limit of normal) and abdominal imaging by contrast-enhanced computed tomography (CT).<sup>8</sup> Contrast-enhanced CT was performed for all patients within 72 hours since admission. IPN was diagnosed according to the positive gram stain and culture results of pancreatic or peripancreatic necrotic tissue obtained by means of CT guided fine needle aspiration, or from the first percutaneous drainage or operation. IPN was managed with a minimally invasive based step-up approach.<sup>9</sup> Next step was performed if there was no clinical improvement after 72 hours. Modified nonsurgical procedures included percutaneous drainage and continuous negative pressure irrigation (CNPI). The severity was defined according to the Determinant-Based Classification of Acute Pancreatitis Severity.<sup>10</sup> Fistula was defined as pathological communications that connect any portion of GI tract with the necrotic cavity, the peritoneal space, the retroperitoneal areas, or another internal organ.<sup>11</sup> Diagnosis of GI fistula was based on fistulography, digestive endoscopy, or operative findings.

Data pertaining to the severity of AP, the severity score, CT severity score, interval between onset of AP and admission to our center, interval between onset of AP and detection of GI fistula, location of GI fistula, intervention for GI fistula and IPN, and outcomes were recorded. Continuous data were compared using a Student *t* test, and categorical data were analyzed using a Chi-square test. A *P*-value of <0.05 was regarded as statistically significant. The data analyses were performed using SPSS 20.0 (IBM SPSS Statistics; IBM Corporation; Armonk, NY).

## RESULTS

A total of 928 patients with AP admitted between January 1, 2010 and December 31, 2013 were screened for potential inclusion and 311 of them developed IPN in the disease course. Of the 311 patients, 209 (67.2%) had been diagnosed with IPN before admission, of which 87 (28.0%) patients had percutaneous drainage, 39 (12.5%) patients had open necrosectomy. Only 83 (8.9%) of all AP patients were admitted in our center within 24 hours since onset of symptoms, and 7 of these 83 patients developed IPN. One hundred nineteen of all AP patients were diagnosed with GI fistula and all of them were IPN patients. All these patients were classified as critical or severe AP and most of them developed a critical course (98, 82.4%). Their mean ( $\pm$ SD) age was 45.1 ( $\pm$ 13.7), and 79 (66.4%) of them were male. The median interval between onset of AP and admission to our center was 38 days. Table 1 shows the comparison of baseline characteristics between the patients with GI fistula and those without GI fistula. The patients with GI fistula had more organs failure. Moreover, they likely had higher CT severity score with a certain trend toward significance (*P* = 0.08).

### Pattern of GI Fistulas

In total, 119 patients developed 160 GI fistulas. Fifty (42.0%) patients had GI fistula before transferred to our center. Sixty-one (45.9%) patients of 133 IPN patients who had

drainage and operative before admission in our center were found with fistulas. Of the other 178 patients who did not have drainage and operative in other centers, 58 (15.7%) patients developed GI fistulas. The colonic fistula was the most common form which was found in 72 patients, followed by duodenal fistula which could be seen in 53 patients. Only 1 patient was diagnosed with ileal fistula. Fistula occurred in duodenum in isolation in 28 patients and in colon alone in 42 patients. Isolated gastric and jejunal fistula were observed in only 8 and 5 patients, respectively. The remaining patients demonstrated a combination of fistulas and duodenal combined with colonic fistula was the dominant form unsurprisingly (Table 2). The median (quartile) interval between onset of AP and detection of GI fistula was 54 (37–78) days. One hundred one (84.9%) patients were detected with GI fistula beyond 1 month. Fifty-four (45.4%) patients were detected with GI fistula after performing first open necrosectomy.

### Treatment and Outcome

Fistulas were managed by a similar step-up approach which included percutaneous drainage, CNPI, and open necrosectomy. All fistulas of upper digestive tract, jejunum, and ileum were managed by nonsurgical procedure. Seventy-four (84.1%) of these 88 fistulas closed spontaneously over time after the source of infection was controlled. Others failed to close since the patients died of multiorgan failure or septic shock. Ileostomy or colostomy was performed for 47 (65.3%) colonic fistulas. Twenty-one of the other 25 colonic fistulas managed by nonsurgical procedure closed spontaneously. Their fistula output was adequately drained by CNPI. Parenteral nutrition was used for a transition period and after the sinus tract's formation enteral nutrition was performed continuously (Table 3). The overall mortality was 34 (28.6%) out of 119. Nineteen of these died of multiorgan failure, and the other 15 of septic shock. No death was caused by fistula directly. Table 4 shows the comparison of outcomes between the IPN patients with and without GI fistula. Although patients with GI fistula

**TABLE 1.** Comparison of Baseline Characteristics of AP Patients With IPN

Characteristics	With Fistula (N = 119)	Without Fistula (N = 192)	<i>P</i>
Age, y	45.1 ( $\pm$ 13.7)	47.4 ( $\pm$ 13.0)	0.43
Male sex, no. (%)	79 (66.4)	121 (63.0)	0.63
Cause of AP, no. (%)			0.52
Gallstones	66 (55.5)	103 (53.6)	
Alcohol abuse	11 (9.2)	26 (13.5)	
Other	42 (35.3)	63 (32.8)	
APACHE II score	14.5 ( $\pm$ 5.5)	11.8 ( $\pm$ 5.0)	<0.01*
MODS			0.01*
Median	3	2	
Range	0–12	0–10	
CT severity score			0.08**
Median	10	10	
Range	4–10	4–10	
Time since onset of symptoms			0.045*
Median	38	28	
Quartile	14–65	10.25–52.75	

AP = acute pancreatitis, CT = computed tomography, IPN = infected pancreatic or peripancreatic necrosis, MODS = the multiple organ dysfunction score.

\**P* < 0.05.

\*\**P* < 0.1.

**TABLE 2.** Distribution of Gastrointestinal Fistulas

Location of Fistulas	No. of Patients
Gastric fistula isolated	8
Duodenal fistula isolated	28
Jejunal fistula isolated	5
Colonic fistula isolated	42
Gastric + duodenal fistula	2
Gastric + jejunal fistula	2
Gastric + colonic fistula	7
Duodenal + jejunal fistula	1
Duodenal + ileal fistula	1
Duodenal + colonic fistula	17
Jejunal + colonic fistula	1
Gastric + duodenal + colonic fistula	2
Gastric + jejunal + colonic fistula	1
Duodenal + jejunal + colonic fistula	2

stayed longer in intensive care unit (ICU) and hospital, the mortality between the 2 groups did not differ significantly. However, the death rate in patients with colonic fistula was 25 (34.7%) out of 72, which was significantly higher than that in patients without GI fistula ( $P = 0.039$ ).

**DISCUSSION**

Although GI fistula is a well-recognized complication of AP, it has been reported in limited literature recently. In this study, we reported our experience with GI fistula in AP with IPN in our center. The incidence of GI fistula varied from 3% to 47% in different studies depending on different study population,<sup>2-5,12</sup> but all these studies included small number of cases. In the present retrospective study, we found 119 (38.3%) patients with GI fistula among 311 AP patients with IPN, and the overall incidence in all AP patients in our center was 12.8%.

The fistula of GI tract can be caused by various reasons. Necrosis of bowel may occur concomitantly with the pancreatic or peripancreatic tissue. Furthermore, enzyme-rich fluid and necrosis can lead to vascular thrombosis, which compromise the blood supply of the segmental GI tract, leading to bowel necrosis eventually.<sup>3,5</sup> In our study, all the patients with GI fistula had necrotizing pancreatitis with IPN. With regard to the time of occurrence of GI fistula during the course of AP, 84.9% patients had GI fistula beyond 1 month, which suggests that development of GI fistulas is associated with the long-term effects of the pancreatic or peripancreatic inflammation and infection.

**TABLE 3.** Treatment and Outcomes of Gastrointestinal Fistulas in Acute Pancreatitis

Treatment	Location of Fistulas	No. of Patients	No. of Death
Nonsurgical procedure	Gastric fistula	22	5
	Duodenal fistula	53	12
	Jejunal fistula	12	0
	Ileal fistula	1	1
	Colonic fistula	25	4
Ileo/colostomy	Colonic fistula	47	21

**TABLE 4.** Comparison of Outcomes of AP Patients With IPN

Characteristics	With Fistula (N = 119)	Without Fistula (N = 192)	P
Critical AP, no. (%)	98 (82.4)	129 (67.2)	0.004*
Death, no. (%)	34 (28.6)	42 (21.9)	0.22
Days in ICU			0.001*
Median	29	18	
Quartile	16-50	7-33.75	
Days in hospital			0.001*
Median	48	34	
Quartile	27-75	20-58.25	

AP = acute pancreatitis; ICU = intensive care unit; IPN = infected pancreatic or peripancreatic necrosis.  
\* $P < 0.05$ .

Additionally, surgical intervention may cause GI fistulas as well. It was reported that frequent debridement and controlled open drainage may increase the incidence of intestinal fistulas in 1989.<sup>4</sup> And a study published in 1995 from Mayo Clinic showed that 19 out of 61 (31.2%) patients developed GI fistulas after surgical management while only 4 (6.6%) were found at the time of initial operation.<sup>5</sup> During recent years, the mainstream management of AP with IPN has changed from open necrosectomy to minimally invasive techniques based step-up approach.<sup>9</sup> Our patients were treated by step-up approach but with a similar incidence of GI fistula and 54.6% patients were detected with GI fistula before performing first open necrosectomy. It was also observed previously that the approach for IPN management did not affect incidence of GI fistula.<sup>9</sup> It suggests that at present time step-up approach might not reduce the risk of iatrogenic GI injury. In addition, it had been recommended that severe AP should be treated in multi-disciplinary specialist units, which included ICU specialists, interventional endoscopists, diagnostic and interventional radiologists, and surgeons.<sup>13</sup> The patients who needs operations obviously could be diagnosed with severe AP. Our results showed that 133 of IPN patients had operative procedures before transfer and 45.9% developed fistula as opposed to 15.7% of those transferred in who did not have operation. It might suggest that the operations should be performed in experienced centers.

GI fistula could involve the stomach, duodenum, jejunum, ileum, and colon, either in combination or separately. Same to other studies,<sup>2,4,5</sup> colonic fistula was the commonest form of GI fistulas in our study, which was found in 72 patients and duodenal fistula the second (53 patients). The underlying mechanisms of this phenomenon may include: first, the anatomy characteristics of peritoneal reflection results in colon and duodenal more frequently affected directly. Second, gut ischemia, as a result of low-flow state or hemodynamic response to sepsis, may be more commonly associated with colon. Furthermore, the stomach and small intestine have a much better blood supply, which could provide a protective mechanism for preventing the formation of fistula.<sup>5,7,14</sup>

The methods of managing fistulas are affected by the site of fistula. It has been reported that most upper-gut fistulas could close with time and colonic fistulas may require active intervention.<sup>2,5,15</sup> In our center, fistulas of upper GI tract, jejunum, and ileum usually closed spontaneously with time if infected source could be well controlled while approximately 7 out of 10

colonic fistulas needed to be managed by enterostomy. However, a study which reviewed 43 reports suggested that colonic fistulas which became apparent after percutaneous pancreatic drainage might close spontaneously.<sup>14</sup> Moreover, several reports showed colonic fistula could close with the aid of nonsurgical techniques such as percutaneous drainage and endoscopic therapy.<sup>16–18</sup> In our study, 21 colonic fistula closed spontaneously with conservative management. Our experience is that those excrement can be completely drained by nonsurgical techniques would close spontaneously. Vital signs and imaging examinations could assist to assess whether the drainage was complete.

GI fistula may cause clinical consequences such as GI hemorrhage and sepsis which might lead to death eventually.<sup>2,14</sup> In our study, patients with GI fistula were associated with more severe disease course and suffered more organs failure. On the other hand, GI fistula could potentially benefit the patient by draining IPN into GI tract.<sup>2,19</sup> In persistence to previous studies that suggested GI fistula did not increase mortality,<sup>2,5</sup> the death rate of patients with GI fistula in our study did not differ significantly from those without GI fistula. However, subgroup analyses showed mortality of patients with colonic fistula was significantly higher than that in patients without GI fistula, namely, colonic fistula was related with higher mortality.

There were several limitations in our study. The actual incidence of GI fistula could be lower than ours because the patients admitted to our center were so complicated that most of them had been treated in other facilities for a long time, even with percutaneous drainage or open necrosectomy, and some patients had been diagnosed with GI fistula before transferred. The heterogeneity of our patients and variable lengths of time to referral to our center would impact the reliability of conclusions regarding identification of factors associated with fistula formation and predictors of death. And some data in previous facilities were incomplete. Additionally, it was a single-center retrospective study.

In conclusion, GI fistula is a common observation in patients of AP with IPN. Colonic and duodenal fistulas are the two commonest forms of GI fistula in IPN patients, and most of them could close spontaneously with proper nonsurgical management except approximately 70% of colonic fistulas needing surgical intervention. For the clinical outcome, the occurrence of colonic fistula is associated with worse outcome.

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