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Multiorgan Failure Predicts Mortality in Emphysematous Pancreatitis: A Case Report and Systematic Analysis of the Literature

Vadim Bul, MD¹, Cemal Yazici, MD², Jonas J. Staudacher, MD², Barbara Jung, MD², and Brian Boulay, MD, MPH²

¹Department of Internal Medicine, University of Illinois-Chicago, Chicago, IL

²Division of Gastroenterology and Hepatology, University of Illinois-Chicago, Chicago, IL

Abstract

Emphysematous pancreatitis (EP) is a subtype of acute necrotizing pancreatitis (ANP) characterized by the presence of gas in and around the pancreas. While investigators have studied prognostic factors in ANP, less is known about EP. We aimed to determine predictors of mortality and identify changes in management strategies for emphysematous pancreatitis. A PubMed search was performed to identify cases of EP. Data was gathered about patient demographics, clinical findings, laboratory results, radiological studies, procedures, outcomes and mortality. Collected data was analyzed using univariate and multivariate logistic regression analysis. Including a case from our institution, the study cohort included 64 subjects. The overall mortality rate was 32.8% (21/64). On univariate analysis, age ($p=.019$), hypotension ($p=.007$), gas outside of the pancreas on CT imaging ($p=.003$), initial surgical evacuation ($p=.007$) and the development of multi-organ failure ($p=.008$) were associated with mortality. On multivariate analysis, only the development of multi-organ failure was found to be an independent predictor of mortality ($p=.039$). The overall mortality rate of 32.8% for EP is similar to the mortality rates published for ANP. The development of multi-organ failure in EP is strongly associated with increased mortality. Percutaneous and endoscopic approaches have been replacing surgical interventions.

Keywords

Emphysematous pancreatitis; acute necrotizing pancreatitis; mortality; survival

Introduction

Acute pancreatitis (AP) is responsible for approximately 1.2 million emergency room visits per year in the United States and approximately 75% of these patients will require admission¹. The estimated annual cost associated with hospitalizations for AP is approximately \$2 billion per year¹. The diagnosis of acute pancreatitis depends on the

Corresponding Author: Cemal Yazici, M.D, University of Illinois at Chicago, Department of Medicine, Division of Gastroenterology, 840 South Wood Street, Suite 718E, Chicago, IL USA 60612, Telephone: 312-996-0141, Fax: 312-996-5103.

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presence of two of three criteria: imaging suggestive of acute pancreatitis, serum amylase and/or lipase greater than three times the upper limit of normal, and epigastric abdominal pain suggesting pancreatic involvement².

While most cases of acute pancreatitis will resolve with conservative management and pain control, up to 20% of patients hospitalized with AP will develop severe disease defined as persistent organ failure lasting more than 48 hours². While several prognostic criteria have been developed to predict disease severity such as the Balthazar³ and Ranson⁴ scoring systems, BISAP score⁵, APACHE-II score⁶ and recently modified Marshall criteria^{2,3}, these scoring systems have not been uniformly clinically accepted. When necrosis of the pancreas is found on imaging, the case can become classified as acute necrotizing pancreatitis (ANP). Studies have shown that patients with ANP tend to have longer hospital stay and greater morbidity and mortality compared to patients with interstitial edematous pancreatitis^{7,8}. Furthermore, previous investigations have demonstrated that the percentage of pancreatic necrosis correlated with decreased survival⁹ and multi-organ failure in the setting of pancreatic sepsis. Approximately 10–40% of patients with acute necrotizing pancreatitis (ANP) will have infected tissue¹⁰. When infection and necrosis are both present, mortality rates can be as high as 50–70%^{11,12}.

Emphysematous pancreatitis (EP) is a subtype of ANP where gas is present in and around the infected, necrotic pancreas^{13,14,15}. Although individual case reports and case series of EP have been published in the literature with a mortality rate of 10%¹⁴ to 36%¹⁶, no systemic analysis has yet been performed to characterize this patient population and to identify risk factors associated with mortality. We hypothesized that the presence of organ dysfunction (a surrogate for severe injury) would be associated with increased mortality while non-surgical interventions (endoscopic and percutaneous) would be associated with decreased mortality. We performed a systematic analysis, including the data from a recent case at our institution, to test our hypothesis and better define clinical features of EP, identify predictors of mortality and determine the impact of non-surgical interventions.

Case Report

A 55 year old male with a history of insulin dependent diabetes mellitus, cholelithiasis requiring cholecystectomy, appendectomy and alcohol-induced pancreatitis presented to an outside hospital for abdominal pain, nausea and vomiting. His initial labs were notable for a lipase of 4000 U/L and acute kidney injury with Cr of 1.6 mg/dL. The patient had a Computed Tomography (CT) abdomen and pelvis showing peripancreatic fat stranding suggestive of acute pancreatitis. After several days, the patient developed a fever and was placed on piperacillin-tazobactam. Blood cultures obtained prior to the initiation of antibiotics grew out *Klebsiella pneumoniae*. Because of continued fevers, a repeat CT scan was performed which showed the development of a pancreatic abscess (Figure 1A). Repeat labs were within normal limits except for an elevated total bilirubin of 2.5 mg/dl and an alkaline phosphatase level of 210 U/L. A third CT scan showed extensive pancreatic inflammation and air consistent with emphysematous pancreatitis and an abscess in the lesser sac measuring 6.6 × 4.7 cm. At this point, his antibiotic was switched to meropenem and he was transferred to our facility.

Upon arrival the patient had a heart of 102 beats per minute with otherwise normal vital signs. He was still complaining of abdominal pain, nausea and vomiting and on exam had epigastric tenderness to palpation without rebound or guarding. Abnormal labs included a leukocytosis of $16,500 \times 10^3/\mu\text{L}$, alkaline phosphatase of 296 U/L, and an albumin of 2.0 g/dL. Amylase and lipase were both 10 U/L. A CT scan at our facility showed progression of his emphysematous pancreatitis with pseudocyst formation along the anterior aspect of the pancreatic tail (Figure 2B). Since the patient remained hemodynamically stable, the decision was made to defer intervention on his pancreas and he was discharged on levofloxacin and metronidazole. Two months after his initial arrival at our hospital, he underwent an upper endoscopic ultrasound showing a 70 mm single compartment, thick walled pancreatic cyst without septae in the pancreas which was endoscopically drained. An endoscopic necrosectomy with removal of residual necrotic debris was also performed (Figures 2A–F). He tolerated the procedure well without any post-procedural complications. Cultures from these procedures grew out *Candida glabrata* and *Klebsiella pneumoniae* and he was discharged on a course of Trimethoprim-Sulfamethoxazole, Metronidazole, and Fluconazole. A subsequent CT scan showed complete resolution of the pancreatic necrosis (Figure 1C). He continued to follow-up in our clinic, gained 10 pounds and did not require further hospitalizations for pancreatitis.

Methods

A PubMed search was performed to identify previous cases of EP using the search terms “emphysematous pancreatitis”, “pancreatitis, gas”, “acute necrotizing pancreatitis, gas”, “acute necrotizing pancreatitis, emphysema”, “acute necrotizing pancreatitis, abscess”. All reports that were published prior to September 2015 were identified and reviewed. Cases that met the inclusion criteria (the presence of gas in the pancreas demonstrated either radiographically or on post-mortem analysis in the setting of symptoms of acute pancreatitis) were included. Data on age, gender, report date, symptoms and vitals on presentation, existing co-morbidities (diabetes mellitus, history of pancreatitis or cardiac disease and prior abdominal surgery), alcohol use, imaging findings, serum leukocyte count, liver function tests, amylase and lipase levels, hemoglobin levels, microbiology results, use of antimicrobial agents, percutaneous and surgical interventions, the presence of organ failure, mortality and length of stay (LOS) were collected. Cases of emphysematous pancreatitis that occurred following instrumentation or drug-induced cases were excluded from analysis.

A systematic analysis was done using the data obtained from previously reported cases and a recent case from our center. Statistical analysis was completed using SPSS v. 22.0 (SPSS Inc, Chicago, IL). Chi-Square or Fisher exact tests were used for categorical data. T-test was used for parametric and Mann-Whitney U test was used for non-parametric testing when appropriate. Subsequently, a multivariate logistic regression analysis was completed to determine the predictors of survival.

Results

Literature search

We identified 63 cases of EP fitting criteria through our literature search. With the addition of our case the study size reached 64 subjects.

Baseline demographics of study population

The mean age of study population was 60.3 $\pm$ 15.7 years. The study cohort included 13 females and 50 males with one case not specifying gender. The average duration of symptoms prior to presentation was 5.6 $\pm$ 11.5 days. Fifty nine percent of subjects had history of alcohol use, 47.8% had diabetes, 30% had previous abdominal surgery, 20.8% had prior episode of pancreatitis and 15% had gallstones. Information on race was not available.

Clinical characteristics of EP subjects who died during hospitalization versus discharged

Of the 64 cases included in our analysis, 21 patients died during hospitalization, resulting in an overall mortality of 32.8%. Age was significantly higher in EP subjects who died compared to EP subjects who survived (66.9 $\pm$ 13.7 vs. 57.1 $\pm$ 16.9 years, $p=.019$) (Figure 3). There were no significant differences in regards to gender (30% female vs. 16.7% female, $p=0.19$), history of diabetes mellitus ($p=.56$), alcohol abuse ($p=0.33$), previous pancreatitis ($p=.32$) or abdominal surgery ($p=.48$) among those who survived versus died (Figure 3).

As shown in table 1, the following categorical variables were seen in significantly higher number of subjects who died compared to those who were discharged: gas outside of the pancreas (86.7% vs. 40.6%, $p=.003$), the development of hypotension (58.3% vs. 10.5%, $p=.007$), multi-organ failure (92.3% vs. 43.8%, $p=.008$), and initial surgical intervention (71.4% vs. 35.0%, $p=.007$). The cohort of patients who survived were significantly more likely to undergo initial percutaneous drainage than those who did not (50% vs. 15%, $p=.008$). There was a trend towards increased frequency of acute kidney injury ($p=.06$) in subjects who did not survive while the presence of two or more SIRS criteria ($p=.42$) did not defer between the two groups. There were no significant differences in the frequency of hyperbilirubinemia ($p=.29$) or elevated transaminases ($p=.09$) between two groups. The average length of symptoms was not statistically significantly different between the two groups (8.73 $\pm$ 22.0 vs. 2 $\pm$ 3.5 days, $p=.17$).

In regards to management, subjects who were diagnosed with EP after the publication of ACG guidelines in 2013 had initial percutaneous intervention more often compared to subjects diagnosed with EP before 2013 (71.4% vs. 29.3%, $p=.007$). Microbiological data of pancreatic fluid samples was available in 40/64 patients (Table 2). The most commonly identified organisms were *Escherichia Coli* ($n=14$) and *Clostridium Perfringens* ($n=12$). Of the cases with available data, 9 subjects had more than one organism grown on pancreatic fluid culture. There was no significant association between types of identified organisms on blood culture ($p=.55$) or pancreatic tissue cultures ($p=.30$) and mortality. Of the cases with antibiotic information available, 100% were treated with antibiotics against gram negative organisms and 93% were treated for gram positive organisms. Too few cases reported data

on duration of antibiotics and length of time to initiation of antibiotics; therefore, no additional analysis was performed.

Predictors of mortality

A multivariate logistic regression analysis was performed to identify possible variables associated with mortality. The following variables were used in the multivariate analysis using entry method: age, gender, multi-organ failure, initial percutaneous drainage and initial surgical drainage. Due to missing data, 27 subjects remained in final analysis. Among these variables only the development of multi-organ failure was found to be a significant predictor of mortality ($p=.038$) whereas age ($p=.059$), initial percutaneous drainage ($p=.999$), initial surgical drainage ($p=.708$), and gender ($p=.999$) were not.

Discussion

Pathogenesis

Emphysematous pancreatitis is characterized by the presence of gas in and/or around the pancreas in the setting of infected pancreatic tissue. The most common organisms associated with emphysematous pancreatitis are gram negative anaerobes including *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter* species^{14,16} with *Clostridium perfringens* being the most common gram positive pathogen^{17,18,19}. Infectious organisms can translocate into the pancreas via hematogenous or lymphatic dissemination, biliopancreatic reflux²⁰ or through direct translocation through enteropancreatic fistulas¹⁴. Patients with diabetes are thought to be at increased risk because of their impaired host vascular and tissue response²¹ and their hyperglycemic state which allows gas producing organisms to ferment glucose into carbon dioxide and hydrogen gas¹¹.

Diagnosis and differential

Prior to the advent of CT, cases were either diagnosed via X-ray, intra-operatively or post-mortem. An X-ray showing gas in the abdomen is a relatively non-specific finding as this gas can be intraluminal or extraluminal gas. Findings suggestive of EP on X-ray are extrinsic compression of the stomach, increased distance between stomach and transverse colon and presence of non-convalescing gas bubbles on serial imaging^{22,23}. Currently, most cases of EP are diagnosed via CT imaging¹⁹. Parenchymal non-enhancement accompanied by multiloculated gas is essentially diagnostic of infected pancreatic necrosis²⁴. Although CT contrast is not needed to diagnose air in the pancreas, it can help to diagnose complications of infected pancreatic necrosis and abscess formation^{12,25}. The classic radiological finding associated with emphysematous pancreatitis is gas in and around the pancreas, commonly in the lesser sac¹⁴.

However, air in the pancreas in itself is not diagnostic of EP. There are several other causes of air in the pancreas that should be considered as these tend to have a more benign course and require less aggressive management^{11,25}. The most common mimicker of EP is the presence of an enteropancreatic fistula. This can often occur in the setting of a ruptured pancreatic pseudocyst or as a complication of phlegmonous pancreatitis. These fistulas, when connected to the gastrointestinal lumen at the duodenum, jejunum or colon, can

themselves lead to pancreatic infection^{12,25,26}. When suspected, fluoroscopy or imaging using water-soluble contrast material can be used to evaluate for this possibility. Other non-infectious etiologies of air in the pancreas include pancreatic biopsy^{27,28}, gall stone pancreatitis²⁹, surgical instrumentation or therapeutic embolization of malignancies³⁰, duodenal diverticulum, a patent ampulla of Vater and penetrating duodenal ulcers¹⁴. The collections of gas in the setting of an abscess tend to have a mottled appearance on CT whereas gas in the setting of therapeutic tissue embolization can have a more linear or branching pattern³⁰.

Treatment options

While intravenous fluids and pain control have been accepted as the mainstay of acute pancreatitis treatment for many years, the usage of interventional procedures for complicated acute pancreatitis cases has evolved over the past couple decades. In previous years, it was felt that gas in and around the pancreas required emergent surgical operation. However, in the early 2000s, several studies showed percutaneous drainage was associated with decreased mortality when compared to open necrosectomy for acute necrotizing pancreatitis^{31,32,33}. Subsequent investigations suggested that medical management alone without any procedural intervention could even be considered in certain cases of infected pancreatic necrosis^{10,13,16,34,35}. Since then, there have been numerous publications supporting a conservative management strategy for infected pancreatic necrosis^{36,37}. Unfortunately, due to the rarity of the condition, none of these published papers have looked exclusively at emphysematous pancreatitis.

Since emphysematous pancreatitis is a subset of infected pancreatic necrosis, treatment should consist of antibiotics in addition to intravenous fluids, pain control and nutritional support with percutaneous intervention being determined on a case by case basis. In stable patients with infected necrosis, drainage should be delayed preferably for at least four weeks to allow for liquefaction of the contents and the development of walled off necrosis³⁸. In patients who have refractory symptoms or other indications for emergent surgery such as catastrophic intra-abdominal hemorrhage, visceral perforation or the development of abdominal compartment syndrome, minimally invasive surgery is preferred to open necrosectomy³⁹.

Expected outcomes

Outcomes with infected pancreatic necrosis (IPN) have drastically improved with the advent of broad spectrum antibiotics and other supportive care equipment. Mortality rates with IPN have decreased from 80% in the 1980s⁴⁰ to the current rate of 8%⁴¹. In the largest study comparing EP and IPN (11 cases of EP and 46 cases of IPN), *Wig et al*¹⁴, no statistically significant difference in rate of mortality was found between the two groups of patients. In *Wig et al* study, the authors found a 36% mortality rate of EP¹⁴ while in *Nadkarni et al* study, the authors found a 10% mortality rate¹⁶. The difference in survival rate between these studies is most likely related to the difference in percentage of surgical intervention as in the *Wig et al* study¹⁴, 100% of patients underwent surgical intervention whereas in the *Nadkarni et al* study¹⁶, only 11% underwent surgery. The patients were otherwise similar in computed tomography severity index (CTSI), age, gender, and microorganisms isolated. The

overall mortality rate in our study was 32.8% and the mortality rate was significantly decreased in patients undergoing initial percutaneous drainage compared to those undergoing initial surgical management (15% vs. 71.4%, $p=.007$). Our findings further corroborates the decreased mortality in patients initially managed with percutaneous drainage found in the previous two studies^{14,16}. In 2010, a landmark study by *van Santvoort et al* was published in the New England Journal of Medicine which showed a statistically significant decrease in mortality using a step-up approach to acute necrotizing pancreatitis³⁷. In 2013, the ACG used this study as part of the evidence supporting the new guidelines for the management of acute pancreatitis which recommended avoidance of surgical intervention². Our analysis showed that patients diagnosed with EP after the 2013 ACG guidelines² were released were significantly more likely to undergo initial percutaneous intervention compared to initial surgery (71.4% vs. 29.3%, $p=.007$).

Study findings

Although older age, the development of multi-organ failure, initial surgical intervention, and gas both in and outside of the pancreas were associated with increased mortality in univariate analysis, the only independent predictor of mortality in multivariate analysis was multi-organ failure. In our study, a history of diabetes mellitus was not associated with increased mortality. However, we noted that patients without a documented history of diabetes who developed hyperglycemia during their acute illness ($n=9$) had 100% mortality. There are two hypotheses to explain this finding. The first possible explanation is that patients with new onset hyperglycemia during acute pancreatitis had a larger percentage of pancreatic necrosis causing dysregulation of glucose levels. Unfortunately too few cases included information about percentage of pancreatic necrosis for us to quantify it during our analysis. The second explanation is related to the known phenomenon of hyperglycemia in the setting of severe sepsis. While the mortality rate in cases with hyperglycemia was higher than the overall mortality rate (64% vs. 32.8%), too few cases reported data on hyperglycemia to allow us to perform a meaningful statistical analysis.

Upon analysis of microbiology, no single organism was associated with increased mortality. As shown in table 2, the majority of bacteria isolated were gram negative enteric organisms. Unexpectedly, almost half of cases had gram positive organisms present on culture, most commonly *Clostridium perfringens*. The vast majority of patients were placed on broad spectrum antibiotics both against gram negative and gram positive organisms. Unfortunately, there was not sufficient data to evaluate time to initiation and duration of antibiotics.

Limitations

There are several limitations to our study. First, despite our review being the most comprehensive to date, the study size remains small and this may lead to decreased power to detect variables which could affect the survival. Secondly, there may be other factors that we could not analyze due to the retrospective design of our study and lack of data in previously published case reports. Thirdly, the data we collected provides a time-point analysis only and we do not have any long-term follow up data.

Conclusion

Emphysematous pancreatitis is a subtype of ANP with resultant gas formation and systemic toxicity. It has been associated with high rates of morbidity and mortality in the past and it has been decreasing over the past decade as confirmed by our study. Through our comprehensive systematic analysis, we revealed that management of EP has shifted from early surgery towards more conservative measures including advanced supportive care and earlier interventions including percutaneous drainage and endoscopic therapy. The only independent predictor of survival was multi-organ failure which correlates well with the notion that advanced supportive care and decreased surgical intervention improves survival. Our analysis did not identify any co-morbid conditions or specific organisms that were associated increased mortality. In conclusion, EP is an important diagnosis to consider in patients with abdominal pain that are toxic-appearing and have evidence of pancreatic emphysema on imaging as early supportive care and conservative management using the step-up approach can be crucial for improving survival.

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Figure 1. CT scans showing evolvement of pseudocyst in setting of emphysematous pancreatitis

A. Peripancreatic fat stranding with evidence of emphysematous pancreatitis with possible early pseudocyst formation.

B. Enlargement and inflammation of the pancreatic head. Pancreatic body and tail severely expanded with numerous foci of air consistent with emphysematous pancreatitis. A 5.0×3.6 cm pseudocyst along the anterior margin of pancreatic tail with a few small foci of air.

C. Cystogastrostomy stents in place. Pancreatic fluid collections completely drained.

Figure 2. Endoscopic images of necrosectomy procedure demonstrating resolution of necrosis

- A. Accumulation of bloody purulent drainage and some small amounts of solid debris through cystogastrostomy tract prior to endoscopic access of the tract.
- B. Post-dilatation cystogastrostomy tract.
- C. Large area of necrosis and inflammation of large cyst with areas of necrotic inflammatory changes involving portion of cavity wall.
- D. View of partially necrotic cyst from endoscope advanced through cystogastrostomy tract. Cyst cavity measured approximately 12 cm in diameter.
- E. Post- partial necrosectomy endoscopy imaging shows large amount of viable, pink tissue with some areas of inflammation and necrosis of tissue located near former location of cyst.
- F. After 2nd half of procedure with completion of necrosectomy showing large amount of viable, pink tissue with irregular cavity wall but no further evidence of necrotic tissue.

Figure 3. A comparison of baseline demographics between patients who died during hospitalization versus survived

Only age was significantly different between the two groups ($p < 0.05$ for all variables except age).

TABLE 1

A Summary of the Variables That Were Found to be Significantly Different Between the Subjects Who Survived Versus Died

	Survived, n (%)	Died, n (%)	<i>P</i>
Age, mean (SD), y	57.1 (16.9)	66.9 (13.7)	.019
Hypotension	2 (10.5)	7 (58.3)	.007
Gas outside of pancreas on CT	13 (40.6)	13 (86.7)	.003
Lack of initial percutaneous drainage	19 (50)	17 (85)	.008
Initial surgery	14 (35)	15 (71.4)	.007
Development of multi-organ failure	7 (43.8)	12 (92.3)	.008

The percentages (in parentheses) are based on subjects in each group who had available data on these particular variables.

Data presented as n (%) unless otherwise indicated.

SD; standard deviation.

TABLE 2

The Most Commonly Identified Microbiological Organisms on Culture of Pancreatic Body Fluids (N=40)

Species	No. Patients (%)
<i>Escherichia coli</i>	14 (35)
<i>Clostridium perfringens</i>	12 (30)
<i>Klebsiella pneumoniae</i>	4 (10)
<i>Citrobacter spp.</i>	3 (7.5)
Unreported	3 (7.5)
<i>Enterobacter faecium</i>	2 (5)
<i>Fusobacterium</i>	2 (5)
<i>Pseudomonas aeruginosa</i>	2 (5)
<i>Staphylococcus aureus</i>	2 (5)
<i>Acinetobacter baumannii</i>	1 (2.5)
<i>Bacteroides spp.</i>	1 (2.5)
<i>Campylobacter showae</i>	1 (2.5)
<i>Candida albicans</i>	1 (2.5)
<i>Candida glabrata</i>	1 (2.5)
<i>Mycobacterium tuberculosis</i>	1 (2.5)
<i>Staphylococcus epidermidis</i>	1 (2.5)
<i>Streptococcus sanguinis</i>	1 (2.5)
<i>Streptococcus viridians</i>	1 (2.5)
2 or more organisms	9 (22.5)