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# Risk Factors for the Development of Intra-Abdominal Fungal Infections in Acute Pancreatitis

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## Abstract

**Objectives—**Intra-abdominal fungal infections (AFI) complicating acute pancreatitis arise in the context of pancreatic necrosis. Our goal was to determine which risk factors contribute to AFI in patients with acute pancreatitis.

**Methods—**Records were reviewed from 479 non-transfer patients admitted to our medical center with acute pancreatitis from 1985–2009. Using multivariable regression models, risk factors for AFI were identified.

**Results—**Out of 479 patients admitted with acute pancreatitis, 17 patients were subsequently found to have an AFI and 3 of these patients expired. The mean length of stay for patients with an AFI was 24 days and 76% were admitted to the intensive care unit. Patients with AFI were more likely to have received prophylactic antibiotics on admission (OR 1.7, 95% C.I. 1.2–2.3), TPN within 7 days of admission (OR 1.4, 95% C.I. 1.1–1.7) or to have necrosis on CT scan within 7 days of admission (OR 1.4, 95% C.I. 1.1–1.7). Multivariable regression models identified admission antibiotic use (OR 1.6, 95% C.I. 1.4–1.8) as the strongest predictor of AFI.

**Conclusion—**Admission antibiotics are the biggest risk factor for the development of intra-abdominal fungal infections in acute pancreatitis. Prophylactic antibiotics to prevent infected necrosis should therefore be discouraged.

### Keywords

pancreatitis; fungal infection; intra-abdominal; intra-bacterial; necrosis

## INTRODUCTION

Acute pancreatitis is a common condition resulting in over 200,000 hospital admissions annually (1,2,3). Based on the Atlanta Classification it is divided into two categories: mild and severe and more recently it has been modified to include a subset of severe pancreatitis

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termed “moderately severe pancreatitis” which is defined by the presence of transient organ failure, local complications or exacerbation of co-morbid disease (4,5). Severe pancreatitis occurs in approximately 15–20% of patients and is defined as persistent organ failure greater than 48 hours (6,7). Mortality rates associated with severe pancreatitis are as high as 20% (7). Infected pancreatic necrosis has been shown to have a higher mortality rate with a mean average of 30% (range 14–69%) when compared to patients with sterile necrosis (8). Of these infections, bacterial, fungal or both are the etiological agents.

From reported literature, the incidence of intra-abdominal fungal infections (AFI) are quite variable from 5–68.5% but carry significant morbidity and mortality rates (9). *Candida* species are the most commonly involved with *C. albicans* the most frequently isolated in the setting of infected necrosis. AFIs complicating acute pancreatitis generally arise proportionately to the extent of pancreatic necrosis, although risk factors for the development of AFI are not well characterized.

The primary goal of this study was to determine which risk factors contribute to AFI in patients with acute pancreatitis. We hypothesized *a priori* that prophylactic antibiotic use and the extent of pancreatic necrosis would be the most important risk factors.

## METHODS

Patients presenting directly to Dartmouth Hitchcock Medical Center (DHMC), an academic tertiary care hospital in Lebanon, New Hampshire, from 1985–2009 with a diagnosis of acute pancreatitis were identified retrospectively by using International Classification of Diseases, Ninth Revision, codes (ICD-9 codes). Only non-transferred patients were included in this study. A primary diagnosis of acute pancreatitis at admission was also required for inclusion. Acute pancreatitis was defined as per the 1992 Atlanta Classification, which required 2 of the following 3 features: abdominal pain characteristic of acute pancreatitis, elevated serum amylase and/or lipase levels greater than 3 times the upper limit of normal, and characteristic findings on trans-abdominal ultrasound or abdominal computed tomography (CT) (4).

Electronic and paper medical records were reviewed and abstracted data included patient characteristics (age, gender, Charlson comorbidity score), process measures (admission antibiotics, total parenteral nutrition (TPN), need for surgery and/or endoscopic retrograde pancreatography (ERCP), and clinical outcomes (presence of systemic inflammatory response (SIRS), organ failure, presence of intra-abdominal bacterial or fungal infection, length of hospital stay (LOS), need for ICU admission and death). SIRS was defined by the presence of >2 of the following criteria: pulse >90 beats per minute, respirations >20 breaths per minute or PaCO2 <32 mmHg, temperature >100.4 F or <96.8 F and white blood cell count >12,000 or <4,000 cell/$mm^3$. Organ failure was defined per the 1992 Atlanta Classification as having at least one of the following: systolic blood pressure <90 mmHg, PaO2 on room air <60 mmHg, serum creatinine >2.0 mg/dL, and gastrointestinal bleed >500mL/h. If not recorded, these values were assumed to the not present for purposes of the study. Severe acute pancreatitis (SAP) was defined as having the presence of SIRS, developing organ failure present for more than 48ours, and/or having evidence of pancreatic

necrosis on abdominal CT; all other patients were classified as having mild or interstitial pancreatitis. The volume and type of IV fluids administered were recorded from initial presentation in the emergency department through 72 hours into the hospitalization by using nursing administration documentation. Antibiotic use was deemed positive if the antibiotics prescribed at admission were used specifically for the treatment of pancreatitis.

The study used a retrospective design. Descriptive statistics were used to characterize the population and are reported as means, standard deviations, and 95% confidence intervals. The two-tailed Fisher's exact test was used to compare categorical variables, and a student's t-test was used to compare continuous variables. An unadjusted logistic regression model to determine ORs followed by a multivariable model to account for potential confounders was built to assess for blood glucose normalization. An alpha level of 0.05% was set for statistical significance. All statistical analysis was performed using Microsoft EXCEL (Microsoft Corporation, Redmond, WA) and Graphpad (Graphpad Software, Inc., San Diego, CA).

The primary study outcomes were the presence of a culture-confirmed intr-abdominal fungal infection and the risk factors associated with this type of fungal infection.

## RESULTS

Out of 479 patients admitted to DHMC for acute pancreatitis, 17 patients (3.6%) were subsequently found to have an intra-abdominal fungal infection and 3 of these patients expired (0.6%). The baseline characteristics of the two groups are displayed in Table 1. Patients with AFIs were more likely to have SIRS on admission and be given admission antibiotics.

Important clinical outcomes are shown in Table 2. ICU admission, the use of TPN, pancreatic necrosis and intra-abdominal bacterial infections were all more common in those with developed AFI. The mean length of stay for patients with AFI was 24 days and 76% were admitted to the intensive care unit. C. *albicans* was the most frequently encountered organism, followed by C. *tropicalis* and C. *krusei*. 2/17 of the patients underwent debridement of infected pancreatic necrosis and subsequently developed AFIs.

Table 3 demonstrates the univariate and multivariate analyses to determine risk factors for AFI. Patients with intra-abdominal fungal infections were more likely to have received prophylactic antibiotics on admission (OR 1.7, 95% C.I. 1.2–2.3), TPN within 7 days of admission (OR 1.4, 95% C.I. 1.1–1.7) and to have necrosis on CT scan within 7 days of admission (OR 1.4, 95% C.I. 1.1–1.7). The degree of necrosis (<50% vs. >50% glandular necrosis) was not found to be more predictive or risk. Aggressive fluid resuscitation (greater than 1/3 of 72 hour IV fluids given within the first 24 hours- OR 0.9, 95% C.I. 0.7–1.3), age >60 years, or gender were not protective against the development of AFI. Multivariable regression models identified admission antibiotic use (OR 1.6, 95% C.I. 1.4–1.8) as the strongest predictor of AFI.

## DISCUSSION

AFI is a serious complication of SAP with an associated increase in morbidity and mortality. From this study it was observed that prior antibiotic is the strongest predictor of AFI (OR 1.6, 95% C.I. 1.4–1.8). These data lend support to guidelines recommending against the initiation of prophylactic antibiotics at admission in severe acute pancreatitis.

Three prior studies showing a strong relationship between antibiotic exposure and associated AFI in patients with severe acute pancreatitis also support this recommendation (10,11,12). Another study, however, showed that exposure to shorter duration of antibiotics with a median time of 6 days proved to be less likely to develop AFI (13). Current guidelines for the treatment of SAP do not recommend the use of prophylactic antibiotics to prevent infection in patients with sterile pancreatic necrosis, which should decrease the risk of developing primary pancreatic fungal infections (6).

Another risk factor for AFI identified in this study was TPN exposure within 7 days of admission; although this was not validated on the multivariate model. With respect to TPN use, is thought that intestinal mucosal atrophy with translocation of intraluminal bacteria results in alteration of bacterial flora thus increasing the risk for AFI. This has been corroborated by a previous study (14). In vitro studies have also shown that C. *albicans* species have flourished in hyperalimentation solutions containing certain amino acids and lipid emulsions (15).

Much like prior studies, our study population was observed to have C. *albicans* being the most frequent organism encountered, followed by C. *tropicalis* and C. *krusei* (10,11). Aggressive fluid resuscitation, male gender and the degree of pancreatic necrosis seen on CT scan were not protective or predictive against the development of AFI. Although we do know that severe necrotizing pancreatitis has a higher risk for AFI than mild cases of pancreatitis, one would have expected to see a decrease risk in patients with more aggressive fluid resuscitation (16).

One of the weaknesses of this study is that the data was collected retrospectively which can lead to certain biases. For example, not every patient with AFI had pancreatic necrosis, so there may have been another intervention – a central venous catheter for example – that could have introduced an AFI that was not necessarily related to pancreatic necrosis. Examples such as these support the risk of possible misclassification bias. However there are many strengths of this study including the fact that the data collectors were blinded to the study. In addition, this study involved a relatively large data and that all patients were directly admitted to a single institution, making incomplete data points less common. Furthermore we were not able to obtain accurate data about the length of use or type of antibiotic; therefore our exposure variable is not well characterized.

Although rare, intra-abdominal fungal infections are a source of considerable morbidity and mortality. Because the prophylactic use of antibiotics on admission is the best predictor for the development of AFI, they should be avoided in patients with severe acute pancreatitis – whether interstitial or necrotic disease is present. Although a trend has begun to support this

recommendation, future published clinical guidelines should consistently reinforce this message.

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## Table 1

Baseline characteristics of patients with and without intra-abdominal pancreatic fungal infections

| | Intra-abdominal Fungal Infection | No Intra-abdominal Fungal Infection | p value |
|---|---|---|---|
| **Number** | 17 | 462 | |
| **Age (years)** | 63 | 53 | 0.050 |
| **Male gender (%)** | 35 | 48 | 0.605 |
| **Charlson Score** | 2.3 | 2.6 | 0.700 |
| **Etiology (%)** | | | 0.063 |
| **Alcohol** | 41 | 37 | |
| **Gallstones** | 0 | 16 | |
| **Idiopathic** | 47 | 28 | |
| **Triglycerides** | 0 | 2 | |
| **Post-ERCP** | 0 | 4 | |
| **Other** | 12 | 13 | |
| **Admission SIRS (%)** | 24 | 64 | **<0.001** |
| **Admission BUN** | 23 | 20 | 0.520 |
| **Admission Organ Failure (%)** | 24 | 9 | 0.065 |
| **Admission Antibiotics (%)** | 64 | 18 | **<0.001** |

Bold text indicates statistically significant result

## Table 2

Outcomes of patients with and without intra-abdominal pancreatic fungal infections

| | Intra-abdominal Fungal Infection | No Intra-abdominal Fungal Infection | p value |
|---|---|---|---|
| **Number** | 17 | 462 | |
| **Mean Length of Hospitalization (days)** | 24 | 17 | 0.382 |
| **ICU Admission (%)** | 76 | 27 | **<0.001** |
| **Volume of IV Fluids in first 72 hours (ml)** | 3,267 | 2,791 | 0.462 |
| **TPN during Hospitalization (%)** | 59 | 22 | **0.002** |
| **Pancreatic Necrosis (%)** | 47 | 3 | **<0.001** |
| **Persistent Organ Failure (%)*** | 42 | 32 | 0.984 |
| **Intra-abdominal Bacterial Infection (%)** | 35 | 3 | **<0.001** |
| **Death (n)** | 3 | 19 | **0.038** |

Bold text indicates statistically significant result

* Defined as >72 hours following admission

## Table 3

Unadjusted and adjusted Odds Ratios for risk factors for intra-abdominal fungal infection

| Intervention | Unadjusted Odds Ratio (95% C.I.) | Adjusted Odds Ratio (95% C.I.)* |
|---|---|---|
| **Admission Antibiotics** | **1.7 (1.2–2.3)** | **1.6 (1.4–1.8)** |
| **Admission SIRS** | 1.1 (0.5–1.6) | ~ |
| **TPN during Hospitalization** | **1.4 (1.1–1.7)** | 1.1 (0.9–1.3) |
| **Pancreatic Necrosis** | **1.4 (1.1–1.7)** | 1.3 (0.7–1.9) |
| **Persistent Organ Failure** | 0.9 (0.3–1.6) | **~** |

Bold text indicates statistically significant result