

Review

Pancreatitis in Solid Organ Transplant Patients: A Review of the Literature

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Abstract

Acute pancreatitis is a highly morbid condition, which is widely recognized and well-defined in the general population. In this article, we summarized the current literature on acute pancreatitis in the setting of solid organ transplant, including patients who are listed for or have undergone transplantation. The incidence of acute pancreatitis in the solid organ transplant patient population ranges from 1-35%. Rates are lowest in cardiac and liver transplant patient populations and highest in the kidney and pediatric intestine transplant populations. The literature is summarized by organ transplant type, including cardiac, lung, pancreas, kidney, intestine, and liver. Our review suggests that providers should have a high index of suspicion for acute pancreatitis in the solid organ transplant population in order to mitigate the morbidity associated with this disease in a highly vulnerable patient population.



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1. Introduction

Acute pancreatitis is one of the most common gastrointestinal disorders worldwide [1, 2], with an incidence that varies widely and is estimated to be approximately 5-73 cases per 100,000 persons [2, 3]. In the United States, there are approximately 270,000 hospital admissions per year for acute pancreatitis, costing an estimated \$2.5 billion [2, 3]. The mortality associated with severe cases, often associated with multisystem organ failure, is estimated to be as high as 50% [4-6]. Acute pancreatitis is most commonly caused by gallstones or alcohol [7]. Other causes include hypertriglyceridemia, endoscopic retrograde cholangiopancreatography (ERCP), genetics, medications, and pancreatic duct injury [8-11]. Minor causes of acute pancreatitis include biliary sludge and microlithiasis, biliary obstruction, infection, and vascular disease [12-15].

While acute pancreatitis is widely recognized and well described in the general population, it is less well characterized in the solid organ transplant patient population. In this study, we summarize the current literature on acute pancreatitis in the solid organ transplant population, including patients who are listed for or have undergone transplantation.

2. Methods

A literature review was conducted to identify studies examining pancreatitis in patients who are listed for or have undergone solid organ transplantation, including cardiac, lung, pancreas, kidney, small bowel, and liver. PubMed was queried for the following terms: “pancreatitis cardiac transplant,” “pancreatitis lung transplant,” “pancreatitis pancreas transplant,” “pancreatitis kidney transplant,” “pancreatitis renal transplant,” “pancreatitis small bowel transplant,” “pancreatitis intestinal transplant,” “pancreatitis liver transplant,” and “pancreatitis transplant.” The term “transplantation” was also used in place of the word “transplant” but led to no different search results. The results were listed in order of “best match” and results 1-40 were examined. This literature search was conducted from February 1, 2019 through March 31, 2019. The abstracts and papers from these searches were compiled, and the pertinent articles are included in this review.

3. Results

In this review, we examined the current literature on acute pancreatitis in solid organ transplant patients, including those who are on waitlists as well as those who have previously undergone solid organ transplantation. Specifically, we examined acute pancreatitis in cardiac, lung, pancreas, kidney, intestine, and liver transplant patients. While we present the current literature, as described above, there is a notable paucity of data in several of the solid organ transplant fields.

3.1 Cardiac Transplantation

Patients who have undergone cardiac transplantation have been shown to have a higher rate of acute pancreatitis when compared to patients who underwent other cardiac procedures. In a retrospective case-control study of over 24,000 patients, Herline et al examined acute pancreatitis after cardiac procedures, including cardiac transplantation. They found a significantly higher rate of acute pancreatitis in the cardiac transplant patients compared to those who had undergone other cardiac procedures (3% vs 0.1%, $p < 0.01$). Further, they found that patients with pancreatitis had significantly higher APACHE II scores compared to those cardiac transplant patients who did not have pancreatitis [16].

The presentation of acute pancreatitis is noted to be occasionally atypical in this patient population. Some describe the presentation crypto-somatic acute pancreatitis, as the typical symptoms are masked presumably, at least in part, due to immunosuppression [17, 18]. Lin et al describe the atypical presentation of a patient with acute hemorrhagic pancreatitis after cardiac transplant. The patient's presentation of acute pancreatitis was further complicated by the fact that he additionally had right heart failure with associated congestive liver dysfunction [17]. Stefaniak et al describe a patient who presented with more typical symptoms of nausea, emesis, and abdominal pain three years after cardiac transplantation. The patient was ultimately diagnosed with acute pancreatitis and pancreatic pseudocysts, which were successfully percutaneously drained [18]. Both patients recovered well from these episodes. In a case series, von Stumm et al describe three patients who had undergone cardiac transplantation and subsequently developed acute pancreatitis. All three patients presented with more typical symptoms, including epigastric pain and nausea. Two of these patients were ultimately found to have pancreatic pseudocysts, which were successfully drained with pigtail drains. The third patient developed a pancreatic abscess and underwent exploratory laparotomy and pancreatic necrosectomy. All patients recovered [19].

3.2 Lung Transplantation

There is a paucity of data on acute pancreatitis in the lung transplant population. There is some evidence for the effects of pancreatic insufficiency on post-transplant outcomes, however, pancreatitis is not well-studied. A systematic review by Koutsokera et al, including 54 studies, sought to identify pre-transplant factors that were associated with mortality after lung transplantation in patients with cystic fibrosis. They found that there was no difference in mortality after lung transplantation between the patients with pancreatic insufficiency and those without pancreatic insufficiency [20].

3.3 Pancreas Transplantation

Pancreatitis is often described as the second most common complication after pancreas transplantation. It frequently occurs in conjunction with pancreas graft rejection and is seen in an estimated 20-60% of rejected allografts [21, 22]. The estimated incidence of acute pancreatitis ranges from 16-35%, and presumed causes include ischemia-reperfusion injury, trauma, biopsy, sepsis,

medications, and infections. Acute pancreatitis frequently presents with abdominal pain, abdominal tenderness on exam, and fever, as seen in the general population [23-26].

Pancreas graft pancreatitis may be classified as acute or chronic, and acute pancreatitis may be sub-classified as early or late. Early acute pancreatitis occurs within the first three months following pancreas transplant and is associated with high rates of graft loss, estimated to be 78-91%. Late pancreatitis occurs greater than three months after transplantation and is a rare cause of graft loss. Chronic pancreatitis is often difficult to distinguish from chronic rejection and is associated with an estimated rate of 4-10% graft loss [24].

Van Dellen et al studied the incidence of and factors associated with transplant graft pancreatitis in rejected pancreas allografts. In their retrospective review of 196 patients at a single institution, they reported that of the 44 rejected allografts in their patient population, 27 patients (61%) had pathology findings consistent with pancreatitis. There was no difference in rates of rejection between patients with and without pancreatitis (26% and 18% respectively, $p = 0.7$). Interestingly, they found no patient factors were statistically significantly associated with graft pancreatitis, including donor age, BMI, donation after brain or circulatory death, cause of death (intracranial hemorrhage, subarachnoid hemorrhage, road traffic accident, other), ischemia time, enteric drainage or bladder drainage [22].

Cornejo-Carrasco et al performed a retrospective review of 238 pancreas transplants at a single institution, aiming to identify the frequency and causes of re-operation in pancreas transplant patients. In their patient population, there were 61 re-operations (61%), 58 of which were early and three of which were late. Pancreatitis was the third most common cause for re-operation, following bleeding and pancreas graft thrombosis, and was seen in 3% of the patients [27].

Hesse et al performed a randomized controlled trial to examine the use of low-dose octreotide after pancreas transplantation with enteric drainage. In this cohort of 40 pancreas transplant recipients, 35 were pancreas-kidney transplants and 5 were pancreas transplants. Patients were randomized to receive low-dose octreotide (0.1mg subcutaneously at the time of operation and three times daily for 7 days) or no octreotide. Pancreatitis was seen in one patient in the octreotide group and no patients in the no octreotide group. This difference was not statistically significant ($p = 0.46$) [25].

Two studies, one case report and one case series, describe pancreatic panniculitis in the pancreas transplant population. Pancreatic panniculitis is a rare cutaneous manifestation of pancreatic disease, occurring in 0.3-3% of patients with pancreatic disease. Patients typically present with painful, erythematous nodules, most frequently on the lower extremities. These lesions may ulcerate or drain a sterile oily fluid and are rarely associated with arthritis and/or serositis. Biopsy of the lesions show "ghost cells" (anucleated adipocytes with thickened cell membranes) and a mixed inflammatory cell infiltrate with areas of calcification. After presenting with these symptoms, the patients were ultimately diagnosed with acute pancreatitis, occasionally resulting in graft loss. The studies suggest that pancreatic panniculitis may be a rare manifestation of pancreatic graft pancreatitis and possibly rejection [28, 29].

3.4 Kidney Transplantation

Acute pancreatitis after kidney transplantation is well-described, with case reports by Dr. Thomas Starzl dating back to 1964 [30, 31]. The incidence of acute pancreatitis in renal transplant recipients is estimated to be 1-14% [30-34], with complications including pancreatic abscess in up to 50% of the cases [35].

Risk factors associated with acute pancreatitis in this population, include co-morbidities (such as PCKD and impaired lipid metabolism [30]), peritoneal dialysis [35], hypercalcemia [33, 36], infectious causes (such as cytomegalovirus or varicella zoster virus) [30, 33, 37, 38], and immunosuppressive mediations [30, 32, 33, 39-44]. Multiple studies describe an increased risk of acute pancreatitis with cyclosporine or corticosteroids [32, 39, 40]. Case reports describe acute pancreatitis associated with everolimus [32], sirolimus [42], and tacrolimus [43]. There is conflicting evidence regarding the association between azathioprine and acute pancreatitis in this patient population [31, 33, 39-41, 45]. Interestingly however, alcohol and cholelithiasis have not been shown to be associated with acute pancreatitis in this patient population [40, 41]. Further, low-dose octreotide showed no association with acute pancreatitis [25].

Similar to pancreatitis in pancreas transplant recipients, pancreatic panniculitis has been described as a sign of underlying pancreatitis in the renal transplant population [28, 29].

The mortality rate associated with acute pancreatitis in renal transplant recipients is estimated to be as high as 60% and is likely higher in cases of necrotizing pancreatitis [30, 32, 41, 46-48]. However, one study suggests that acute pancreatitis is not associated with 1-year patient or graft survival [35].

3.5 Intestinal Transplantation

Acute pancreatitis is the most common pancreaticobiliary complication after intestinal transplantation, including small or large bowel transplant and multivisceral transplant. It occurs in approximately 6% of the adult intestinal transplant population [49, 50] and in up to 25% of the pediatric intestinal transplant population [51]. Notably, pancreatitis may be seen in the graft and/or the native pancreas [49]. Risk factors for pancreatitis in this population are unclear, but may include ischemia and reperfusion injury [49]. There is contradicting evidence regarding the association of histidine–tryptophan–ketoglutarate (HTK) or University of Wisconsin solution with acute pancreatitis, with one study suggesting a higher rate of acute pancreatitis with HTK and one showing no difference [49, 52]. Graft loss in intestinal transplant may be as high as 50%. One study suggests that acute pancreatitis was seen in 11% of patients suffering graft loss [53].

3.6 Liver Transplantation

The estimated incidence of post-liver transplant pancreatitis is 3-8% with an associated 38-63% mortality [54, 55]. Factors associated with, and possible causes of, acute pancreatitis can be broadly classified into four groups including infection, medications, surgical factors, and post-transplant complications [54-56]. Prior studies suggest that there is a statistically significant association between Hepatitis B virus as the indication for transplantation and post-transplant pancreatitis (seen in up to

30% of cases). Cytomegalovirus, tuberculosis, and varicella zoster virus have been reported to be associated with acute pancreatitis in case reports, though this association has not been seen in larger studies to date. Surgical factors that may be associated with acute pancreatitis include extensive dissection near the pancreas, the type of biliary reconstruction (e.g., higher rate of acute pancreatitis with Roux-en-Y stented choledochojejunostomy when compared to donor-recipient duct-to-duct anastomosis over a T tube), repeat liver transplantation, use of aorto-hepatic interposition grafts, and the duration of cardiopulmonary bypass [54, 55]. Biliary complications, such as leak or stricture, are often managed with endoscopic retrograde cholangiopancreatography (ERCP) frequently with sphincterotomy. Pancreatitis is a well-documented complication of ERCP in the general population and is similarly seen in the liver transplant recipient population. ERCP is estimated to account for 1-16% of post-liver transplant pancreatitis [54], and one study found that 6% of post-liver transplant patients undergoing ERCP later developed acute pancreatitis [56]. Other biliary tract procedures, such as T-tube manipulation and percutaneous trans-hepatic cholangiography may also lead to acute pancreatitis [54]. Medications may be cited as a cause of pancreatitis in the liver transplant recipient population. There is inconclusive evidence regarding the association of acute pancreatitis with various immunosuppressant drugs, however, increasing amounts of IV calcium chloride appear to be associated with increasing rates of acute pancreatitis [54, 55].

While post-liver transplant patients with acute pancreatitis may present with typical symptoms, their presentation may also be masked. Acute panniculitis, as previously mentioned, has similarly been reported in liver transplant patients [57].

Regardless of the etiology of acute pancreatitis, it is associated with increased graft failure as well as increased morbidity and mortality in the liver transplant population [54, 58]. In a study previously conducted at our institution, there was no difference in graft failure or death rates (7% vs. 7%) at 30-days post-transplant in patients with peri-transplant pancreatitis (defined as 30 days pre- or post-transplant) when compared to controls. However, graft failure or death rates were significantly higher in the acute pancreatitis group at both 60- and 90-days post-transplant (33% vs. 13% and 44% vs. 27%, respectively). The overall hazard ratio (HR) for graft failure or death in the acute pancreatitis group compared to controls was 2.28 ($p < 0.01$), and the HR in the post-transplant acute pancreatitis group was slightly higher at 2.57 ($p < 0.01$) [58].

The management of acute pancreatitis is well-described in the general population, though there are no clear guidelines for specific management strategies in the liver transplant recipient population [1-4]. Case reports describe minimally invasive management of pancreatic pseudocyst and pancreatic necrosis, as would be seen in the general population [59, 60]. Mejia et al studied the outcomes of pancreatic surgery in over 3,000 liver transplant recipients. Pancreatitis was the indication for surgery in 0.6% of this patient population. The authors found that the 30-day complication rate was 78% and the 3-, 12-, and 24-month survival was 78%, 48%, and 24%, respectively. These results demonstrate the high rates of morbidity and mortality associated with pancreatic surgery in this patient population [61].

4. Discussion

While acute pancreatitis is common and often leads to high morbidity in the general patient population, the presentation of and outcomes associated with acute pancreatitis in the solid organ transplant population is variably studied, with the largest body of literature in the kidney transplant population. This study describes the current literature to date, and the results show a high rate of morbidity and mortality associated with acute pancreatitis in the solid organ transplant patient population. It can be assumed that acute pancreatitis is at least as morbid in this patient population as in the general population. Further, it has been suggested that immunosuppression can mask the typical symptoms of acute pancreatitis, leading to a more difficult and/or delayed diagnosis. Yet, there is inconclusive evidence regarding the association between acute pancreatitis and the use of immunosuppressant medications. Taken together, these findings suggest that providers should have a high index of suspicion for acute pancreatitis in the solid organ transplant population to attempt to mitigate the morbidity associated with this disease in a highly vulnerable patient population.

Author Contributions

Dr. Danielle Graham and Dr. Fady Kaldas designed the presented review. Dr. Danielle Graham and Dr. Takahiro Ito collected the data and performed the literature review. Dr. Danielle Graham took the lead on writing the manuscript, which all authors edited. Dr. Fady Kaldas and Dr. Ronald Busuttill supervised the project. All authors provided critical feedback and contributed to the final manuscript.

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Competing Interests

The authors have declared that no competing interests exist.

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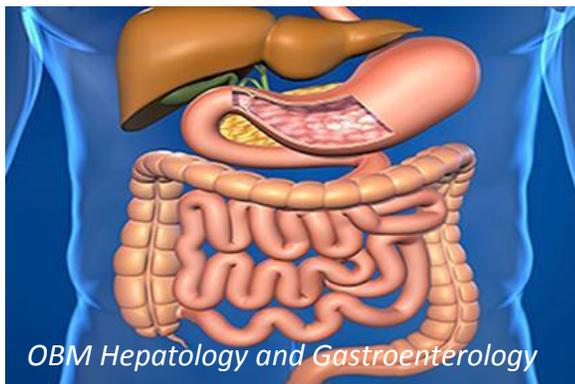
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