DR. JONATHAN A FRIDELL (Orcid ID : 0000-0002-8708-1506)
DR. BENJAMIN J ULRICH (Orcid ID : 0000-0002-2729-1798)

Article type : Review Article

Pancreas transplantation for Cystic Fibrosis: A Frequently Missed Opportunity

Jonathan A. Fridell[1]

Molly A. Bozic[2]

Benjamin J. Ulrich[1]

Andrew J. Lutz[1]

John A. Powelson[1]

[1]Department of Surgery, Division of Abdominal Transplant Surgery, Indiana University School of Medicine, Indianapolis, IN
[2]Department of Pediatric Gastroenterology, Riley Hospital for Children, Indianapolis, IN

Jonathan A. Fridell, MD, FACS
Professor of Surgery
Chief of Abdominal Transplant Surgery
Director of Pancreas Transplantation
Indiana University School of Medicine
550 N University BLVD, Room 4601

This is the author's manuscript of the article published in final edited form as:

Fridell, J. A., Bozic, M. A., Ulrich, B. J., Lutz, A. J., & Powelson, J. A. (2021). Pancreas transplantation for Cystic Fibrosis: A Frequently Missed Opportunity. Clinical Transplantation, e14371. https://doi.org/10.1111/ctr.14371

Indianapolis, IN 46202
Email: jfridell@iupui.edu
T: 317-944-4370
F: 317-968-1254

Data Availability: Data available on request from corresponding author

Keywords:
Cystic Fibrosis, Pancreas Transplant, Cystic Fibrosis Related Diabetes, Liver Transplant, Lung Transplant

Acknowledgement: The authors would like to thank Angelika Gruessner from the International Pancreas Transplant Registry for providing additional data and statistical interpretation regarding pancreas transplantation in recipients with cystic fibrosis and pediatric recipients of pancreas transplants

Abstract:

Cystic fibrosis (CF) is an inherited autosomal recessive disorder. Despite optimized therapy, the majority of affected individuals ultimately die of respiratory failure. As patients with CF are living longer, extra-pulmonary manifestations may develop including pancreatic failure, which manifests as exocrine insufficiency, and CF related diabetes (CFRD). Both of these can be managed through pancreas transplantation. Pancreas transplantation is usually performed in combination with another organ, most often with a kidney transplant for end-stage diabetic nephropathy. In the CF patient population, the two settings where inclusion of a pancreas transplant should be considered would be in combination with a lung transplant for CF pulmonary disease, or in combination with a liver for CF related liver disease with cirrhosis. This report will discuss this topic in detail, including a review of the literature regarding combinations of lung/pancreas and liver/pancreas transplant.

Keywords: Pancreas Transplant, Liver Transplant, Lung Transplant, Cystic Fibrosis, Cystic Fibrosis Related Diabetes,

Cystic fibrosis (CF) is an autosomal recessive disorder characterized by impaired chloride transportation across epithelial membranes resulting in dehydrated viscous secretions that obstruct ducts causing infection and ultimately end-organ damage (1). Worldwide, approximately 70,000 individuals are affected by CF, with an incidence of nearly 1 in 3000 live births in Caucasian populations (2, 3). CF presents as a multisystem disorder affecting not only the pulmonary system, but gastrointestinal, hepatobiliary, endocrine and reproductive systems as well.

Mucus retention and chronic infection in the airways of patients with CF results in progressive respiratory failure (4). Since discovery of the CF gene, remarkable new therapies have been developed which have improved the function of the cystic fibrosis transmembrane regulator (CFTR) (3). These therapeutic advances along with partnerships between the Cystic Fibrosis Foundation, federal agencies, industry, academic institutions and patients have resulted in improved care and subsequent life expectancy for CF patients (5). Mortality rates for patients with cystic fibrosis have dramatically improved over the years, with a median predicted survival age of 46.2 years in 2019 according to the Cystic Fibrosis Foundation Patient Registry (6). Pulmonary disease remains the leading cause of mortality and morbidity. Lung transplantation is reserved as an option for patients with advanced pulmonary disease. The first lung transplant for a patient with CF was performed in 1983. CF patients currently account for approximately 15% of all adult lung transplants representing a significant portion of the post-lung transplant population (7). With improving therapies and lung transplantation, patients with CF are living longer but are struggling more with other end-stage organ dysfunction syndromes, including CF related cirrhosis, cystic fibrosis related diabetes (CFRD) and pancreatic exocrine insufficiency (PEI) which are now becoming larger contributors to morbidity and mortality in these patients.

Pancreatic insufficiency and CFRD

Pathologist Dorothy Anderson first described pancreatic involvement in cystic fibrosis along with the lung and intestinal manifestations in the 1930's (8). In the pancreas of patients with CF, abnormalities in chloride transportation result in decreased volume and increased acidity of pancreatic fluid, creating a thickened mucous secretion. This results in pancreatic duct obstruction, inflammation and pancreas atrophy, which in turn compromise both the exocrine and endocrine pancreatic functions

(9-12). PEI is very common presenting in nearly 85% of patients with CF by the time they reach one year of age. Once diagnosed with PEI, patients should receive supplemental pancreatic enzyme replacement therapy to prevent fat malabsorption and malnutrition. Usually this is a lifelong treatment for these patients (13).

Endocrine pancreas dysfunction manifesting as CFRD is one of the most common extra-pulmonary comorbidities afflicting patients with CF. Sharing some characteristics with both Type I and Type II diabetes, CFRD is considered a unique disease characterized by insufficiency of insulin with an insidious rather than acute onset, increased prevalence with age, and frequently requiring relatively high doses of insulin. Most patients with CFRD have a normal weight or are underweight compared to the obesity commonly seen in patients with type II diabetes (14, 15). CFRD has been reported in only approximately 10% of children with CF by 10 years of age but up to 40-50% by adulthood (16). Known risk factors for CFRD include increasing age, female gender, PEI, hepatobiliary disease, organ transplantation, and corticosteroid use (17). Correlating impaired exocrine and endocrine function, almost 80% of individuals with PEI early in life develop CFRD by mid adulthood (18, 19).

The mainstay of treatment for CFRD is insulin therapy. Other common therapies used in Type II diabetes such as oral hyperglycemic medications have not been shown to be as effective in managing CFRD. Appropriate glucose control has not only been shown to prevent diabetes related complications, but has also been shown to have a positive impact on pulmonary function, nutritional status and overall survival in patients with CFRD(16, 20, 21). Unfortunately, patients with CFRD have a 3.5-fold increase in mortality compared to CF patients without diabetes (16, 19). CFRD is associated with worse lung function, infections, and poorer nutritional status resulting in an overall worse median age of survival regardless of lung transplant status (22, 23). With the emerging development of CFTR modulator and potentiator therapies, which have had a significant impact on the pulmonary health of patients with CF, further studies will be required in order to elucidate the impact of these therapeutic modalities on CFRD.

Pancreas transplantation in patients with CF

Enteric drained whole organ pancreas transplantation in the setting of CF is an attractive solution for CFRD and PEI as it would correct both the endocrine and exocrine deficiencies. Successful pancreas transplantation provides optimized glycemic control independent of insulin administration in diabetic recipients; and the enterically drained pancreatic exocrine secretions would provide improved absorption and nutrition independent of orally administered pancreatic enzymes. Unfortunately, pancreas transplantation in this patient population has not been widely embraced (24). The original and long supported justification for pancreas transplantation in the setting of Type 1 diabetes mellitus was in combination with another organ, almost always a renal transplant for diabetic nephropathy, as these particular recipients have already committed to lifelong immunosuppression. This can either be performed simultaneously from the same donor (simultaneous pancreas and kidney (SPK)) or sequentially (pancreas after kidney (PAK)). It is analogously appealing to include a pancreas allograft in combination with a lung or liver transplant, either simultaneously or sequentially, in recipients with diabetes using the exact same justification. Clearly, there are situations where patients with CF will become candidates for either a lung or liver transplant, and would also particularly benefit and be potential candidates for a pancreas transplant to treat underlying CFRD with or without PEI.

Of note, pancreas transplantation in recipients with CF is one of very few indications for pediatric pancreas transplantation. Typically, as described above, pancreas transplantation is performed along with a kidney for end stage diabetic nephropathy, which is typically unlikely to manifest before adulthood. Rarely, a pediatric candidate with a different etiology for end stage renal failure as their primary indication for renal transplantation may also coincidentally have Type 1 diabetes mellitus. According to data from the International Pancreas Transplant Registry (IPTR), out of 33,541 pancreas transplants in diabetic recipients with or without a kidney transplant (SPK, PAK or pancreas transplant alone (PTA)) reported to the registry, only 39 were in recipients <18 years old (22 SPK, 13 PTA and 4 PAK) with more than half of those performed before 1995 (personal communication with Angelika Gruessner from the IPTR). In this context, it would be appropriate to consider the 9 simultaneous liver and pancreas transplants (as well as two multivisceral transplants and one pancreas intestine transplant) in pediatric recipients with CF to be a very substantial volume of pediatric pancreas transplants. For this reason, the procedures described here would require

appropriately size matched donor organs, a surgical team comfortable performing transplant surgery in pediatric recipients and full pediatric hospital, nursing and pediatric subspecialty support in order to optimize outcomes.

Lung and Pancreas Transplantation for CF

The combination of lung and pancreas transplantation for patients with CF is particularly appealing, but has only been performed on very rare occasions. The only report of simultaneous bilateral sequential lung and pancreas transplantation in recipients with CF was from Indiana University, and included a series of three patients (25). Despite initial success in those three cases, none of the three actually went on to enjoy long-term survival (26). Their postoperative courses were complicated by surgical issues for both the abdominal and thoracic portions of the operation, and by episodes of rejection and resistant infections. Two of these patients required relaparotomy: the first patient for Distal Intestinal Obstruction Syndrome (DIOS, also known as Meconium Ileus Equivalent) and the third patient for hematoma. The second and third patients had technical complications from the lung transplant procedure, one of which required allograft pneumonectomy. Survival in this cohort was 20 months, 44 months and 6 months respectively, according to the order that the cases were presented in the original report. After this series was published, organ allocation policies for lung and liver transplantation in the United States were modified to prioritize the sickest potential recipients, making it very difficult to obtain a suitable simultaneous pancreas allograft from an ideal donor while the patient remains well enough and has enough reserve to undergo the combined transplant surgery. Based on this and presumably the initial outcomes, there have been no additional reports of simultaneous lung and pancreas transplantation, with the exception of a successful triple transplantation of three simultaneous organs (lung/liver/pancreas) in a recipient with CF from the team from the University of Toronto, Canada (27). In addition to published work, in personal communication with the International Pancreas Transplant Registry, there has been an additional lung/liver/pancreas but no further lung/pancreas transplants.

Pancreatic islet transplantation in the setting of bilateral lung transplantation for CF has been reported several times since the 1990s. There are case and small series reports, but many are from the

same centers, presumably with overlapping patients. The first report was from Geneva, Switzerland of a patient with CF who underwent combined islet-lung transplantation with a modest decrease in insulin requirements to approximately 50% of pre-transplant amounts(28-30). The groups from Strasbourg, France and Geneva, Switzerland subsequently reported on four cases of combined islet-lung transplantation with similar results: modest to no improvement in insulin requirements but increase in c-peptide levels (31-33). There has also been a recent report of islet after lung transplantation achieving insulin independence after the infusion of islets from two donors which was sustained for 1.5 years, following which insulin was resumed(34). Finally, there was a report of a combined liver, lung and islet transplant which, despite the infusion of islets from three separate donors, never achieved insulin independence (insulin requirements decreased from 1.1 to 0.8 units/kg/day after the third infusion)(35). Altogether, there have been perhaps seven cases of islet transplantation reported in the setting of lung transplantation for CF with almost universal failure to achieve insulin independence from the simultaneous donor, but with some increase in c-peptide levels and some improvement in glycemic control and relief from hypoglycemia unawareness. Furthermore, islet transplantation does not address exocrine insufficiency at all. Islet transplantation, however, eliminates the potential surgical complications from pancreas transplantation which may be poorly tolerated in the setting of lung transplantation. In fact, according to the majority of these publications, the primary indication for islet transplant rather than whole organ pancreas in this setting was the belief that CF patients could not tolerate combined thoracic and abdominal transplant procedures. As an alternative approach, the group from Indiana University has recently published a case report of a successful SPK transplant after lung transplant in a patient with CF. This sequential transplantation is an ideal option, providing all of the advantages of a whole organ pancreas transplant while allowing the recipient an opportunity to completely recover from lung transplantation prior to undergoing pancreas transplantation. This approach also circumvents the issues introduced by the newer lung allocation policies by providing opportunities for the acceptance of an offered lung allograft even if the pancreas is not suitable(26).

Liver and Pancreas Transplantation for CF

With increasing life expectancy among patients with CF, extrapulmonary complications including CF related liver disease and cirrhosis have become more widely recognized. Liver disease develops in no more than one-third of patients with cystic fibrosis. Nevertheless, liver disease and liver failure remain the single most important nonpulmonary cause of death, accounting for about 2.5% of overall cystic fibrosis mortality (36). While many patients with CF will demonstrate elevated liver enzymes throughout their lifetime (37) only 5-10% will develop severe CF related multilobular cirrhosis (38). While the pathophysiology of CF related cirrhosis is not fully understood, it is thought to result from bile duct plugging and inspissated bile, which leads to inflammation and subsequent liver fibrosis (39). CF related cirrhosis is a disease recognized in childhood and adolescence with nearly all cases reported in the first two decades of life (40) with a mean age at diagnosis of 10 years old (41). CF related cirrhosis is characterized by portal hypertension with marked splenomegaly, hypersplenism as well as subsequent complications including varices and ascites (39). End-stage liver disease, liver failure with severe impaired synthetic function, appears late in the course of liver disease in CF patients(42). Approximately 20% of deaths after the diagnosis of cirrhosis result from liver complications and 33% from respiratory complications(43).

Liver transplantation is the second most common transplant procedure offered to recipients with CF and with adequate pulmonary reserve, although there have been several reports of simultaneous lung and liver or heart–lung and liver transplants in recipients with CF(44-46). Liver transplantation alone (independent of lung transplantation) for CF patients with cirrhosis and adequate pulmonary reserve has now become fairly standard with a reported significant survival benefit and improvement in pulmonary status attributed to either improved nutritional status or perhaps decreased shunting and abdominal distension with relief of the portal hypertension and ascites. (47, 48) In reviewing a series of liver transplant recipients with CF from the University of Pittsburgh Medical Center(47), a single case of multivisceral transplantation in a child with CF performed for short gut syndrome secondary to meconium ileus was identified (49). The authors at the time specifically acknowledge the disadvantages of having performed a near total allograft pancreatectomy, depriving the patient of treatment for their exocrine insufficiency and CFRD. Shortly after that, several reports describing simultaneous pancreas and liver transplantation were published with either both organs implanted separately or *en-bloc* (50-54). In 2005, Fridell and colleagues from Indiana University

reported successful simultaneous orthotopic liver and heterotopic pancreas transplantation in two patients, one of which was a pediatric recipient (age 13) (51). Around that time, Young et al. from St-James Hospital in Leeds, UK reported a single case (53) and Mekeel et al from the University of Florida reported a series of three pediatric recipients (52) of simultaneous en-bloc liver-pancreas transplant in the setting of CF. There was one additional case report in 2013 by Henn and colleagues from Leipzig, Germany of a 23-year-old recipient of a simultaneous orthotopic liver and heterotopic pancreas transplantation (54). Of the seven patients described in these four reports, all enjoyed long-term survival with complete independence from insulin and pancreatic enzyme replacement, with only the one from the most recent case report ultimately succumbing to pulmonary complications of CF five years after transplant. In 2014, Bandsma, et al., surveyed 81 pediatric transplant centers and identified 8 simultaneous liver-pancreas transplants performed in patients ranging in age from 12 to 22 years-old (50). With a mean follow-up of 8 months, all patients had restoration of endocrine and exocrine function, although one patient eventually resumed insulin therapy. However, 4/8 (50%) of the patients suffered major post-operative complications including thrombosis of the aortic conduit, superior mesenteric artery thrombosis, one pancreatic leak managed with drainage and one biliary leak managed with endoscopic retrograde cholangiopancreatography placed stents. Two patients experienced episodes of acute cellular rejection. Overall, the recipients of both a liver and a pancreas allograft demonstrated improved nutritional status as manifested by improved z-score and BMI and, at least initially, improved pulmonary status based on FEV1.

In 2016, Usatin and colleagues reported a United Network for Organ Sharing registry data review from 1987-2014. Of the 303 liver transplants performed in patients with CF, only seventeen were in combination with a pancreas transplant with an 88% two-year survival (with one additional lung/liver/pancreas transplant as described previously identified)(24). This study also identified 3 lung-pancreas, 4 SPKs, and 3 PTAs performed in patients with cystic fibrosis, overall including 17 adults and 11 children. In this study, adding a pancreas to another organ transplant did not have an adverse impact on survival. At 2-year follow-up, 26 of the 28 pancreas recipients remained free of insulin. The authors concluded that CFRD is a common sequela of cystic fibrosis and pancreas

transplantation is underutilized as a therapeutic option in patients receiving other organ transplants for this disorder.

On a technical note, it has historically been recommended to consider *roux-en-y* biliary reconstruction in the setting of liver transplantation alone for CF presumably due to the involvement of the native biliary tract in the disease process. If that is the case and the organs are implanted separately (heterotopic pancreas transplant), the pancreatic duodeno-enterostomy can be situated either proximal to or distal to the roux anastomosis(51, 54). For the *en-bloc* transplant technique, the arterial inflow to both organs is via a Y graft reconstruction of the donor celiac and superior mesenteric arteries to the aorta and with anastomosis of the recipient portal vein to the side of the donor portal vein between the superior border of the pancreas and the liver (53) or to the superior mesenteric vein below the neck of the pancreas (52), with a duodeno-jejunostomy for drainage of both allografts. Of note, all of these reports were from a period of time predating significant changes in the liver allocation policy that favor patients with the highest Model for End Stage Liver Disease (MELD) score. Currently, no priority is given to combinations of organs that include the pancreas, meaning that recipients would have to either accept expanded criteria combination organs (i.e. lower quality organs) while they are still lower down on the list but have reserve for a combined operation, or wait until they are substantially sicker and lack reserve in order to have access to the ideal organ combinations. The combination of liver and pancreas should: 1. ideally be performed simultaneously because, unlike combined lung and pancreas transplantation, the liver recipient is already committed to a laparotomy and 2. from the same organ donor for immunological reasons relating to the protective effect of multiple organs of common origin (consider pancreas allograft survival for SPK compared to PAK). Unfortunately, unless something changes regarding prioritization of these organ combinations in allocation policy in the near future, the less attractive alternative solution that we may have to settle for in this setting may mirror our proposed solution for lung and pancreas transplantation and become pancreas after liver transplantation.

Post-operative Management of the Patient with CF

There are several issues related to the transplant recipient's underlying CF that may impact postoperative management. First, all of these recipients have either undergone lung transplantation or

have advanced pulmonary disease, although with adequate reserve to undergo an abdominal procedure. Airway colonization, potentially with resistant organisms, is ubiquitous. Technical complications and delayed graft function are particularly poorly tolerated in this susceptible patient population, so organ selection and meticulous surgical technique are of paramount importance. The goal should be for early extubation whenever possible. This is also another justification for considering pancreas after liver, or pancreas after lung transplantation, rather than simultaneous transplantation because separating the transplant operations in both of these settings results in a pancreas transplant procedure performed in an optimized patient.

DIOS, or Meconium Ileus Equivalent, as mentioned above as a complication seen in one of the simultaneous lung and pancreas transplant recipients, is actually a well described complication following other surgeries in patients with CF, including following lung transplantation (55). It is recommended that a strict and aggressive bowel regimen including N-acetylcysteine be initiated following any operation (particularly abdominal procedures) in order to avoid this. If not avoided, this complication may require operative decompression or bowel resection for inspissated stool.

Conclusions

Pancreas transplantation is a reasonable consideration for patients with CF with CFRD and PEI undergoing liver or lung transplantation. While many centers have embraced simultaneous liver and pancreas transplantation, either *en-bloc* or implanted separately, not many simultaneous lung and pancreas transplants have been performed; although early results were good, long-term survival has been poor. With improving outcomes for pancreatic islet transplantation, simultaneous lung and islet transplantation may emerge as a better alternative, although this will not address the enzyme insufficiency. Yet another alternative may be sequential transplantation of the lung and pancreas transplants, which allows the recipient an opportunity to recover from the pulmonary transplant prior to the pancreas transplant.

References:

1. Rowe SM, Miller S, Sorscher EJ. Cystic fibrosis. N Engl J Med. 2005;352(19):1992-2001.
2. Cystic Fibrosis Foundation. About cystic fibrosis. [Available from: https://www.cff.org/What-is-CF/About-Cystic-Fibrosis.
3. Cogen JD, Ramsey BW. The Changing Face of Cystic Fibrosis. . In: Davis S, Rosenfeld M, Chmiel J, editors. Cystic Fibrosis A Mulit-Organ System Approach Respiratory Medicine Series: Humana Press; 2020.
4. Elborn JS. Cystic fibrosis. Lancet. 2016;388(10059):2519-31.
5. Ramsey BW, Nepom GT, Lonial S. Academic, Foundation, and Industry Collaboration in Finding New Therapies. N Engl J Med. 2017;376(18):1762-9.
6. 2019 Cystic Fibrosis Foundation Patient Registry Annual Data Report.
7. Chambers DC, Cherikh WS, Harhay MO, Hayes D, Jr., Hsich E, Khush KK, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. J Heart Lung Transplant. 2019;38(10):1042-55.
8. Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease: a clinical and pathologic study. Am J Dis Child 1038;56(2):344-99.
9. Kopelman H, Corey M, Gaskin K, Durie P, Weizman Z, Forstner G. Impaired chloride secretion, as well as bicarbonate secretion, underlies the fluid secretory defect in the cystic fibrosis pancreas. Gastroenterology. 1988;95(2):349-55.
10. Kopelman H, Durie P, Gaskin K, Weizman Z, Forstner G. Pancreatic fluid secretion and protein hyperconcentration in cystic fibrosis. N Engl J Med. 1985;312(6):329-34.
11. Wilschanski M, Novak I. The cystic fibrosis of exocrine pancreas. Cold Spring Harb Perspect Med. 2013;3(5):a009746.
12. Wilschanski M, Durie PR. Pathology of pancreatic and intestinal disorders in cystic fibrosis. J R Soc Med. 1998;91 Suppl 34:40-9.
13. Davies JC, Cunningham S, Harris WT, Lapey A, Regelmann WE, Sawicki GS, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis

and a CFTR gating mutation (KIWI): an open-label, single-arm study. Lancet Respir Med. 2016;4(2):107-15.

14. Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care. 2010;33(12):2697-708.

15. Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes. 2018;19 Suppl 27:64-74.

16. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. 2009;32(9):1626-31.

17. Granados A, Hughan KS. Cystic Fibrosis-Related Diabetes. . In: Davis S, Rosenfeld M, Chmiel J, editors. Cystic Fibrosis A Mulit-Organ System Approach Respiratory Medicine Series Humana Press
2020.

18. Kelly A, Moran A. Update on cystic fibrosis-related diabetes. J Cyst Fibros. 2013;12(4):318-31.

19. Lewis C, Blackman SM, Nelson A, Oberdorfer E, Wells D, Dunitz J, et al. Diabetes-related mortality in adults with cystic fibrosis. Role of genotype and sex. Am J Respir Crit Care Med. 2015;191(2):194-200.

20. Moran A, Pekow P, Grover P, Zorn M, Slovis B, Pilewski J, et al. Insulin therapy to improve BMI in cystic fibrosis-related diabetes without fasting hyperglycemia: results of the cystic fibrosis related diabetes therapy trial. Diabetes Care. 2009;32(10):1783-8.

21. Kolouskova S, Zemkova D, Bartosova J, Skalicka V, Sumnik Z, Vavrova V, et al. Low-dose insulin therapy in patients with cystic fibrosis and early-stage insulinopenia prevents deterioration of lung function: a 3-year prospective study. J Pediatr Endocrinol Metab. 2011;24(7-8):449-54.

22. Brennan AL, Geddes DM, Gyi KM, Baker EH. Clinical importance of cystic fibrosis-related diabetes. J Cyst Fibros. 2004;3(4):209-22.

23. Bismuth E, Laborde K, Taupin P, Velho G, Ribault V, Jennane F, et al. Glucose tolerance and insulin secretion, morbidity, and death in patients with cystic fibrosis. J Pediatr. 2008;152(4):540-5, 5 e1.
24. Usatin DJ, Perito ER, Posselt AM, Rosenthal P. Under Utilization of Pancreas Transplants in Cystic Fibrosis Recipients in the United Network Organ Sharing (UNOS) Data 1987-2014. Am J Transplant. 2016;16(5):1620-5.
25. Fridell JA, Wozniak TC, Reynolds JM, Powelson JA, Hollinger EF, Duncan MW, et al. Bilateral sequential lung and simultaneous pancreas transplant: a new approach for the recipient with cystic fibrosis. J Cyst Fibros. 2008;7(4):280-4.
26. Fridell JA, Lutz A, Powelson JA. Simultaneous pancreas and kidney transplant after bilateral lung transplant for a recipient with Cystic Fibrosis. American Journal of Transplantation.in press.
27. Barbas AS, Dib MJ, Al-Adra DP, Goldaracena N, Sapisochin G, Waddell TK, et al. Combined lung-liver-pancreas transplantation in a recipient with cystic fibrosis. J Cyst Fibros. 2018;17(1):e1-e4.
28. Tschopp JM, Brutsche MH, Frey JG, Spiliopoulos A, Nicod L, Rochat T, et al. End-stage cystic fibrosis: improved diabetes control 2 years after successful isolated pancreatic cell and double-lung transplantation. Chest. 1997;112(6):1685-7.
29. Buhler L, Andereggen E, Deng S, Spiliopoulos A, Nicod L, Rochat T, et al. Combined islet-lung transplantation in a cystic fibrosis patient. Schweiz Med Wochenschr Suppl. 1996;79:73S-5S.
30. Cretin N, Buhler L, Fournier B, Caulfield A, Oberholzer J, Becker C, et al. Results of human islet allotransplantation in cystic fibrosis and type I diabetic patients. Transplant Proc. 1998;30(2):315-6.
31. Kessler L, Bakopoulou S, Kessler R, Massard G, Santelmo N, Greget M, et al. Combined pancreatic islet-lung transplantation: a novel approach to the treatment of end-stage cystic fibrosis. Am J Transplant. 2010;10(7):1707-12.
32. Kessler L, Greget M, Metivier AC, Moreau F, Bosco D, Santelmo N, et al. Combined pancreatic islet-lung transplantation with islet percutaneous portal embolization in cystic fibrosis. Transplantation. 2008;85(11):1670-1.

33. Kessler L, Greget M, Metivier AC, Moreau F, Armanet M, Santelmo N, et al. Combined pancreatic islets-lung transplantation in cystic fibrosis-related diabetes: case reports. Transplant Proc. 2010;42(10):4338-40.
34. Spijker HS, Wolffenbuttel BH, van der Bij W, Engelse MA, Rabelink TJ, de Koning EJ. Islet-after-lung transplantation in a patient with cystic fibrosis-related diabetes. Diabetes Care. 2014;37(7):e159-60.
35. Klee P, Dirlewanger M, Lavallard V, McLin VA, Mornand A, Pernin N, et al. Combined Pancreatic Islet-Lung-Liver Transplantation in a Pediatric Patient with Cystic Fibrosis-Related Diabetes. Horm Res Paediatr. 2018;90(4):270-4.
36. Colombo C. Liver disease in cystic fibrosis. Curr Opin Pulm Med. 2007;13(6):529-36.
37. Woodruff SA, Sontag MK, Accurso FJ, Sokol RJ, Narkewicz MR. Prevalence of elevated liver enzymes in children with cystic fibrosis diagnosed by newborn screen. J Cyst Fibros. 2017;16(1):139-45.
38. Colombo C, Battezzati PM, Crosignani A, Morabito A, Costantini D, Padoan R, et al. Liver disease in cystic fibrosis: A prospective study on incidence, risk factors, and outcome. Hepatology. 2002;36(6):1374-82.
39. Leung DH, Narkewicz MR. Cystic Fibrosis-related cirrhosis. J Cyst Fibros. 2017;16 Suppl 2:S50-S61.
40. Lindblad A, Glaumann H, Strandvik B. Natural history of liver disease in cystic fibrosis. Hepatology. 1999;30(5):1151-8.
41. Stonebraker JR, Ooi CY, Pace RG, Corvol H, Knowles MR, Durie PR, et al. Features of Severe Liver Disease With Portal Hypertension in Patients With Cystic Fibrosis. Clin Gastroenterol Hepatol. 2016;14(8):1207-15 e3.
42. Flass T, Narkewicz MR. Cirrhosis and other liver disease in cystic fibrosis. J Cyst Fibros. 2013;12(2):116-24.
43. Feigelson J, Anagnostopoulos C, Poquet M, Pecau Y, Munck A, Navarro J. Liver cirrhosis in cystic fibrosis--therapeutic implications and long term follow up. Arch Dis Child. 1993;68(5):653-7.
44. Wise PE, Wright JK, Chapman WC, Drinkwater DC, Slovis BS, Pierson RN, et al. Heart-lung-liver transplant for cystic fibrosis. Transplant Proc. 2001;33(7-8):3568-71.

45. Zimmerman AA, Howard TK, Huddleston CB. Combined lung and liver transplantation in a girl with cystic fibrosis. Can J Anaesth. 1999;46(6):571-5.
46. Couetil JP, Soubrane O, Houssin DP, Dousset BE, Chevalier PG, Guinvarch A, et al. Combined heart-lung-liver, double lung-liver, and isolated liver transplantation for cystic fibrosis in children. Transpl Int. 1997;10(1):33-9.
47. Fridell JA, Bond GJ, Mazariegos GV, Orenstein DM, Jain A, Sindhi R, et al. Liver transplantation in children with cystic fibrosis: a long-term longitudinal review of a single center's experience. J Pediatr Surg. 2003;38(8):1152-6.
48. Mendizabal M, Reddy KR, Cassuto J, Olthoff KM, Faust TW, Makar GA, et al. Liver transplantation in patients with cystic fibrosis: analysis of United Network for Organ Sharing data. Liver Transpl. 2011;17(3):243-50.
49. Fridell JA, Mazariegos GV, Orenstein D, Sindhi R, Reyes J. Liver and intestinal transplantation in a child with cystic fibrosis: a case report. Pediatr Transplant. 2003;7(3):240-2.
50. Bandsma RH, Bozic MA, Fridell JA, Crull MH, Molleston J, Avitzur Y, et al. Simultaneous liver-pancreas transplantation for cystic fibrosis-related liver disease: a multicenter experience. J Cyst Fibros. 2014;13(4):471-7.
51. Fridell JA, Vianna R, Kwo PY, Howenstine M, Sannuti A, Molleston JP, et al. Simultaneous liver and pancreas transplantation in patients with cystic fibrosis. Transplant Proc. 2005;37(8):3567-9.
52. Mekeel KL, Langham MR, Jr., Gonzalez-Perralta R, Reed A, Hemming AW. Combined en bloc liver pancreas transplantation for children with CF. Liver Transpl. 2007;13(3):406-9.
53. Young AL, Peters CJ, Toogood GJ, Davies MH, Millson CE, Lodge JP, et al. A combined liver-pancreas en-bloc transplant in a patient with cystic fibrosis. Transplantation. 2005;80(5):605-7.
54. Henn C, Kapellen T, Prenzel F, Siekmeyer M, Hau HM, Kiess W, et al. Combined heterotopic liver-pancreas transplantation as a curative treatment for liver cirrhosis and diabetes mellitus in cystic fibrosis. Pediatr Transplant. 2014;18(1):E6-9.
55. Minkes RK, Langer JC, Skinner MA, Foglia RP, O'Hagan A, Cohen AH, et al. Intestinal obstruction after lung transplantation in children with cystic fibrosis. J Pediatr Surg. 1999;34(10):1489-93.