**Chapter 2- Pancreas and Islet Cell Transplantation**

2.1. Induction therapy

Search terms: pancreas transplant OR islet transplant AND induction, pancreas transplant AND alemtuzumab, pancreas transplant AND (basiliximab OR daclizumab), pancreas transplant AND thymoglobulin, exenatide AND islet transplant, etanercept AND islet transplant

Pancreas Transplant

A. Bank JR, Heidt S, Moes DJ, et al. Alemtuzumab induction and delayed acute rejection in steroid-free simultaneous pancreas-kidney transplant recipients. *Transplant Direct*. 2016;3(1):1-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28349124
    a. Cohort study assessing incidence and time to acute rejection episodes (AREs) in 73 SPK transplants receiving either alemtuzumab + steroid free maintenance (tacrolimus + mycophenolate mofetil) or antithymocyte globulin + triple therapy maintenance (tacrolimus + mycophenolate + steroid).
    b. Overall number of AREs at 3 years was significantly lower with alemtuzumab versus ATG induction (26.0% vs 43.5%; adjusted hazard ratio, 0.38; *P* = 0.029). Most AREs (94.6%) with ATG occurred within the first month, whereas 84.2% of AREs with alemtuzumab occurred beyond 3 months.
B. Bazerbachi F, Selzner M, Boehnert MU, et al. Thymoglobulin versus basiliximab induction therapy for simultaneous kidney pancreas transplantation: impact on rejection, graft function, and long-term outcome. *Transplantation*. 2011 Nov 15;92(9):1039-43. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22002345.
    a. Retrospective study of thymoglobulin vs basiliximab induction in SPK transplant recipients between January 2001 and August 2008 at a single center.
    b. Thymoglobulin induction was associated with decreased rejection at 3 months and 1 year posttransplant. Long-term graft function and survival were not different between the two groups.
C. Fernandez-Burgos I, Montiel Casado MC, Perez-Daga JA, et al. Induction therapy in simultaneous pancreas-kidney transplantation: thymoglobulin versus basiliximab. *Transplant Proc*. 2015 Jan-Feb; 47(1): 120-2. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25645787.
    a. Retrospective study of thymoglobulin vs basiliximab induction in SPK transplant recipients between February 2000 and August 2013 at a single center.
    b. Thymoglobulin group had less overall cellular rejection (P=0.045) and improved, though not statistically significant, patient survival at 1, 3, and 5 years follow-up. No difference in pancreas graft survival at any point. Major complications and median length of hospital stay were higher in the basiliximab group.
D. Farney AC, Doares W, Rogers J, et al. A randomized trial of alemtuzumab versus antithymocyte globulin induction in renal and pancreas transplantation. *Transplantation*. 2009 Sep 27;88(6):810-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19920781.
    a. Prospective, randomized, single-center trial comparing alemtuzumab and thymoglobulin induction therapy in kidney and pancreas transplant recipients.
    b. Alemtuzumab was associated with less rates of rejection compared to thymoglobulin.

E. Fridell JA, Mangus RS, Chen JM, et al. Steroid-free three-drug maintenance regimen for pancreas transplant alone: Comparison of induction with rabbit antithymocyte globulin +/- rituximab. *Am J Transplant*. 2018 Dec;18(12):3000-3006. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29738100
    a. Retrospective study of 166 PTX who received induction with rabbit antithymocyte globulin +/- rituximab and maintenance therapy with tacrolimus, sirolimus, and mycophenolate mofetil.
    b. Graft loss at 7 and 90 days were 4% and 5%, and 1-year patient and graft survival were 97% and 91%. Comparing induction with and without rituximab, there was no significant difference in 7- or 90-day graft loss, 1-year patient or graft survival, or in the rate of rejection or infection.
F. Kaufman DB, Leventhal JR, Gallon LG, Parker MA. Alemtuzumab induction and prednisone-free maintenance immunotherapy in simultaneous pancreas-kidney transplantation comparison with rabbit antithymocyte globulin induction- long-term results. *Am J Transplant*. 2006 Feb;6(2):331-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16426317.
    a. Retrospective, non-randomized, single-center study to evaluate alemtuzumab vs thymoglobulin induction with a prednisone free, tacrolimus/sirolimus based immunosuppression protocol.
    b. Long term graft and patient survival, infection and malignant complications and rejection rates did not differ between the groups.
G. Li J, Koch M, Kramer K, et al. Dual antibody induction and de novo use of everolimus enable low-dose tacrolimus with early corticosteroid withdrawal in simultaneous pancreas-kidney transplantation. *Transpl Immunol*. 2018 Oct;50:26-33. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29885442
    a. Cohort study in which 25 SPK recipients received 2 doses of basiliximab and intraoperative thymoglobulin. Thymoglobulin could be redosed within the first week to maintain absolute lymphocyte below 500/µL. All patients were steroid free by POD7. Maintenance immunosuppression included tacrolimus and everolimus.
    b. The BPAR within the first 12 months was 13%. During a median follow-up of 58 months, new-onset diabetes mellitus and renal function deterioration were rare events. No cytomegalovirus activation was encountered. The patients, pancreas and kidney graft survival at 1-year and 5-year was 100% and 94.4%, 95.8% and 95.8%, 100% and 100% respectively.
H. Magliocca JF, Odorico JS, Pirsch JD, et al. A comparison of alemtuzumab with basiliximab induction in simultaneous pancreas kidney transplantation. *Am J Transplant*. 2008 Aug;8(8):1702-10. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18694474.
    a. Retrospective, single-center study of SPK patients using alemtuzumab induction compared with historical controls that received basiliximab.
    b. No difference observed in terms of survival, DGF, EBV/BKV infection, PTLD, or sepsis. Increase in CMV infection in the alemtuzumab-treated group (P=0.002) led to use of a single 30 mg dose of alemtuzumab instead of two doses. Long-term effects remained to be seen.
I. Stratta RJ, Rogers J, Orlando G, et al. 5-year results of a prospective, randomized, single-center study of alemtuzumab compared with rabbit antithymocyte globulin induction in simultaneous

kidney-pancreas transplantation. *Transplant Proc*. 2014;46(6):1928-31. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25131073.

a. Prospective study comparing outcomes in 46 SPK transplant recipients receiving induction with either alemtuzumab or rabbit antithymocyte globulin conducted from February 2005 to October 2008.
b. There was no difference in patient or allograft survival as well as rates of acute rejection at 5 years follow-up between either groups. CMV infection rates were significantly lower utilizing alemtuzumab induction versus rabbit antithymocyte globulin.

J. Uemura T, Ramprasad V, Matsushima K, et al. Single dose of alemtuzumab induction with steroid-free maintenance immunosuppression in pancreas transplantation. *Transplantation*. 2011 Sep 27;92(6):678-85. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/21841541.

a. Retrospective, single-center study of patients who underwent pancreas transplantation (SPK, PAK, or PTA) and received alemtuzumab induction therapy.
b. A single dose of alemtuzumab induction therapy demonstrated patient and graft survival results comparable to other induction agents over median follow-up of 25 months.

K. Zhang R, Florman S, Devidoss S, et al. The long-term survival of simultaneous pancreas and kidney transplant with basiliximab induction therapy. *Clin Transplant*. 2007 Sep-Oct;21(5):583-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17845631.

a. Retrospective, single-center review of SPK patients who received basiliximab induction therapy from March 1998 to August 2005.
b. Basiliximab induction with TAC, MFA, and steroid maintenance can provide good long-term patient and graft outcomes with low incidence of rejection and CMV.

Islet Cell Transplant

A. Bellin MD, Barton FB, Heitman A, et al. Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. *Am J Transplant*. 2012;12(6):1576-83. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22494609.

a. Prospective, multi-center, open-label study of patients undergoing islet cell transplantation from 2002 to 2008. Patients received one of four possible induction regimens.
b. Induction with ATG in combination with a TNF-α inhibitor (etanercept) had higher rates of insulin independence at 5 years comparable which was comparable to pancreas transplant.

B. Faradji RN, Tharavanij T, Messinger S, et al. Long-term insulin independence and improvement in insulin secretion after supplemental islet infusion under exenatide and etanercept. *Transplantation*. 2008;86(12):1658-65. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19104401.

a. Prospective in 9 islet transplants study examining the efficacy of a modified Edmonton protocol with the addition of exenatide and etanercept to induction with daclizumab compared to the standard Edmonton protocol group
b. All patients in the modified protocol group (n=5) had insulin independence at 18 months post islet cell transplantation compared to only 20% in the standard group (n=4)

2.2. Maintenance therapy

Search terms: pancreas transplant AND maintenance, pancreas transplant AND tacrolimus, pancreas transplant AND cyclosporine, pancreas transplant AND sirolimus, pancreas transplant AND everolimus, pancreas transplant AND belatacept, pancreas transplant AND steroid free, pancreas transplant AND steroid withdrawal, Edmonton protocol, islet cell AND immunosuppression, islet transplant AND steroid free, islet transplant AND exenatide

A. Amodu Li, Tiwari M, Levy A, et al. Steroid maintenance is associated with an increased risk of infections but has no effect on patient and graft survival in pancreas transplantation: a retrospective review of the UNOS database. *Pancreatology*. 2015 Sept-Oct;15(5):554-562. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26330202.
    a. Report of an evaluation of UNOS database reviewing adult patients who received pancreas and kidney-pancreas transplants from January 1996 to March 2014 to evaluate the appropriateness of steroid maintenance.
        i. Two groups for evaluation: steroid induction only (n=4391) and steroid maintenance (n=22686).
    b. Evaluation of four-year time periods yielded statistically significant decrease in steroid maintenance and increase in steroid induction only from 1996 to 2014 ($p<0.0001$).
        i. Overall graft failure rate was higher in the steroid maintenance group versus the induction only group ($p <0.0001$).
        ii. Patient survival advantage was observed at 1 and 3 years favoring steroid maintenance. Graft survival advantage was observed at 3 and 5 years favoring steroid maintenance. After correcting for multiple recipient characteristic differences, no difference in patient or graft survival was ascertained.
    c. Statistically significant incidence of post-op infection rates 4.8% in steroid maintenance versus 3.9% in steroid induction only ($p=0.01$).
    d. Data from this review demonstrates that maintenance steroid therapy may have no impact on patient or graft survival with utilization of thymoglobulin induction therapy. Additionally, steroid maintenance may be associated with higher incidence of post-op infections.
B. Bechstein WO, Malaise J, Saudek F, et al. Efficacy and safety of tacrolimus compared with cyclosporine microemulsion in primary simultaneous pancreas-kidney transplantation: 1-year results of a large multicenter trial. *Transplantation*. 2004 Apr 27;77(8):1221-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15114089.
    a. Report of an open-label, multicenter study comparing efficacy and safety of tacrolimus with microemulsion cyclosporine in patients who received SPK transplantation.
        i. Study completed in 10 European centers and one center in Israel. All patients received induction with thymoglobulin, maintenance with mycophenolate mofetil 2-3 grams/day and short-term steroids.
        ii. One-year outcomes reported for 103 patients randomly assigned to tacrolimus (0.2 mg/kg) and 102 patients in microemulsion cyclosporine (7 mg/kg).
    b. Biopsy proven kidney or pancreas acute rejection at one-year were lower with FK arm (27.2%) compared to microemulsion CsA (38.2%), $p=0.09$.

i. Pancreas graft survival was significantly improved with FK (91.3%) compared to microemulsion CsA (74.5%), p<0.0005.
ii. Renal graft survival was similar between arms.

c. Data from this study demonstrate support for FK therapy in patients undergoing SPK due to type 1 diabetes with end-stage renal disease.

C. Bosmuller C, Ollinger R, Sieb M, et al. Tacrolimus monotherapy following alemtuzumab induction in combined kidney-pancreas transplantation: results of a prospective randomized trial. *Ann Transplant*. 2012 Dec 31;17(4):45-51. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/23274323.

a. Report of single center experience with alemtuzumab induction and tacrolimus maintenance therapy compared to thymoglobulin induction with tacrolimus + mycophenolate + steroids maintenance in kidney-pancreas transplant patients.
i. Group A: N=14 of alemtuzumab 30mg + methylprednisolone 500mg intraoperatively then tacrolimus monotherapy
ii. Group B: N=16 of thymoglobulin 8mg/kg intraoperatively with tacrolimus + mycophenolate mofetil (MMF) + steroids (withdrawn at month 3)

*NOTE*: target FK trough levels 12-15 ng/mL in both groups until month 6, then target trough was 6-12 ng/mL

b. Patient survival was 100% in both arms at 1 year; Group A kidney and pancreas graft survival 93% per graft while Group B kidney and pancreas graft survival 100% and 87% respectively.

c. All biopsy proven acute rejection reversible; no acute pancreas graft rejection.

d. Data form this single center experience demonstrated comparable efficacy and safety of alemtuzumab induction and FK maintenance therapy compared to rab thymoglobulin induction with FK+ MMF+ steroids maintenance in kidney-pancreas transplant patients.

D. Brennan DC, Kopetskie HA, Sayre PH, et al. Long-term follow-up of the Edmonton Protocol of islet transplantation in the United States. *Am J Transplant*. 2016 Feb;16(2):509-17. Retrieved from https://www-ncbi-nlm-nih-gov/pubmed/26433206.

a. Report of long term follow up evaluating efficacy and safety of islet transplantation in seven type 1 diabetic subjects from the United States enrolled in international Edmonton Protocol.
i. Intended immunosuppression regimen was sirolimus and tacrolimus, however 6 patients discontinued sirolimus (5 due to mouth ulcers, 1 due to ischemic colitis). These patients were switched to MMF or mycophenolic acid (MPA).

b. Subjects were followed up to 12 years with islet function measured via C-peptide. All seven subjects retained islet function for more than 10 years.
i. One subject insulin independent without diabetic medications
ii. One subject insulin independent for 8 years then had graft failure
iii. Six subjects demonstrated continued islet function with diabetic medications

c. Median hemoglobin A1c of 6.3%. No reports of hypoglycemia, lymphoma, or opportunistic infection.

d. Data from this report support safety of Edmonton Protocol in long-term evaluation even with low rate/duration of insulin independence.

E. Ciancio G, Sageshima J, Chen L, et al. Advantage of rapamycin over mycophenolate mofetil when used with tacrolimus for simultaneous pancreas kidney transplants: randomized, single-center trial at 10 years. *Am J Transplant*. 2012 Dec;12(12):3363-76. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22946986.
    a. Report of randomized, prospective, single-center trial of either mycophenolate mofetil or rapamycin in combination with tacrolimus for maintenance immunosuppression after simultaneous pancreas-kidney transplant.
    b. Between September 2000 to December 2009 the center enrolled 170 patients; n=84 rapamycin and n=86 mycophenolate mofetil.
        i. Dual induction with thymoglobulin (1 mg/kg) total of 5 doses, daclizumab (1 mg/kg) two doses and methylprednisolone 500 mg one dose; low dose maintenance tacrolimus (level 5-7 ng/mL) and corticosteroids.
            - Mycophenolate mofetil 1000 mg BID staring POD #1
            - Rapamycin 4 mg /day starting POD #1 with target level 5-7 ng/mL
    c. Graft and patient survival did not differ between arms, however there were increased rates of biopsy proven acute rejection in the MMFgroup compared to rapamycin at 1 year (88% vs 100%, p=0.001) and at 10 years (92% vs 99%, p=0.01). Increase in rate of rejection were associated with holding MMF due to gastrointestinal or bone marrow toxicity.
    d. Results from this single center experience demonstrate that rapamycin combination with FK was better tolerated with more effective antirejection profile than MMF.

F. Fridell JA, Agarwal A, Powelson JA, et al. Steroid withdrawal for pancreas after kidney transplantation in recipients on maintenance prednisone immunosuppression. *Transplantation*. 2006 Aug 15;82(3):389-92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16906038.
    a. Report of a retrospective single-center review of pancreas after kidney transplants between June 2003 and January 2006 evaluating steroid withdrawal from patients taking prednisone for previous renal transplant.
        i. Induction with thymoglobulin, brief taper of intravenous solumedrol over 4-5 days, and maintenance therapy of tacrolimus and sirolimus
        ii. Intervention: either resume chronic steroid or complete steroid withdrawal
    b. Total of 30 PAK transplants performed in 29 patients: steroid arm n=10 and steroid-free arm n=19. There was one pancreas graft loss and a single mortality in the steroid-free group, but no difference in renal function or infection rates.
    c. Data from this single center review postulate safe withdrawal of steroids in PAK transplant recipients if thymoglobulin utilized for induction with FK and sirolimus maintenance.

G. Froud T, Faradji RN, Pileggi A, et al. The use of exenatide in islet transplant recipients with chronic allograft dysfunction: safety, efficacy, and metabolic effects. *Transplantation*. 2008;86(1):36-45. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18622276.
    a. Report of a prospective study in 16 islet cell transplant recipients given exenatide for allograft dysfunction causing a new insulin requirement post-islet transplantation.
    b. At six months, 3 patients were insulin independent while the other twelve had a statistically significant reduction in insulin requirements as well as an increase in c-peptide.

c. Four patients had to discontinue study medication due to gastrointestinal side effects such as nausea and diarrhea.
d. Results of this study demonstrate that exenatide was well tolerated post-islet transplant with appropriate dose titration allowing for gradual and sustained positive outcomes on glycemic control.

H. Gallon LG, Winoto J, Chhabra D, et al. Long-term renal transplant function in recipient of simultaneous kidney and pancreas transplant maintained with two prednisone-free maintenance immunosuppressive combinations: tacrolimus/mycophenolate mofetil versus tacrolimus/sirolimus. *Transplantation*. 2007 May 27;83(10):1324-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17519781.
   a. Report of a retrospective, single-center, sequential study of 59 SPK transplant patients evaluating impact of long-term renal allograft function of two steroid-free maintenance regimens with tacrolimus.
      i. Induction with thymoglobulin
      ii. FK/MMF arm with n=22
      iii. FK/sirolimus arm with n=37
   b. No significant difference in patient survival (6 years) or ACR between groups. There was increased kidney graft survival in the FK/MMF arm (90.7% vs 70.7%, p=0.09), however this was not found to be statistically significant. Both arms demonstrated similar decline in slope of glomerular filtration. Pancreas survival at 6 years post-transplant was 100% in both arms.
   c. Data from this single center study suggest similar outcomes and a numerically lower incidence of kidney graft survival with maintenance regimen of FK/sirolimus compared to FK/MMF.

I. Gruessner RW, Kandaswamy R, Humar A, et al. Calcineurin inhibitor- and steroid-free immunosuppression in pancreas-kidney and solitary pancreas transplantation. *Transplantation*. 2005 May 15;79(9):1184-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15880067.
   a. Report of a prospective, nonrandomized, observational cohort study of 75 SPK and PTA patients who received alemtuzumab induction with mycophenolate induction and maintenance therapy compared to a historical group of 266 patients that received thymoglobulin induction and tacrolimus maintenance.
      i. Alemtuzumab (4 doses induction and up to 12 doses within first year) with mycophenolate mofetil ( $\geq$ 2 grams/day)
   b. No statistically significant differences in patient or graft survival rates were seen within the first 6 months.
   c. There were higher rates of (reversible) rejection in the SPK recipient study group compared to historical group ($P \geq 0.0003$) and 6 patients in this group were changed to CNI therapy. MDRD and SCr were improved in the study group, but differences did not reach statistical significance.
   d. Results of this study demonstrate alemtuzumab and MMF regimen associated with acceptable rejection rate with potential to eliminate undesired CNI and steroid related side effects, however longer follow up is lacking.

J. Jin J, Jin L, Luo K, et al. Effect of empagliflozin on tacrolimus induced pancreas islet dysfunction and renal injury. *Am J Transplant*. 2017 Oct;17(10):2601-2616. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28422431.
    a. Report of rat model evaluation of SGLT-2 inhibitor empagliflozin on tacrolimus induced diabetes mellitus.
        i. There were six groups of 12 rats each, randomized to receive three weeks of tacrolimus or vehicle via drinking water. Once tacrolimus induced diabetes was confirmed, empagliflozin was added at a dose of 5 or 10 mg/kg. Empagliflozin was also found to have increased urinary glucose compared to vehicle arm.
    b. Empagliflozin decreased SGLT-2 expression in a dose-dependent manner (5mg: $1.6 \pm 0.1$, 10mg: $1.5 \pm 0.5$, $p < 0.05$).
        i. Tacrolimus had twofold increase in SGLT-2 expression in a dose dependent manner: $2.2 \pm 0.1$ vs. $1.0 \pm 0.1$, $p < 0.05$.
        ii. Tacrolimus increased urinary glucose compared to the vehicle group ($198 \pm 26$ vs. $0 \pm 0$ mg/g, $p < 0.05$).
    c. Data from this study show that empagliflozin improved tacrolimus induced hyperglycemia with probable impact on decrease of SGLT-2 expression. Additionally, plasma insulin level increased and islet size recovered.

K. Knight RJ, Podder H, Kerman RH, et al. Comparing an early corticosteroid/late calcineurin-free immunosuppression protocol to a sirolimus-, cyclosporine A-, and prednisone-based regimen for pancreas-kidney transplantation. *Transplantation*. 2010 Mar 27;89(6):727-32. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/20195219.
    a. Report of a nonrandomized, single-center, sequential study of low-immune responder SPK patients (PRA <50%) evaluating triple maintenance immunosuppression (n=20) or sirolimus maintenance with early steroid withdrawal followed by late CNI withdrawal (n=22).
        i. Induction with thymoglobulin
        ii. Triple therapy arm: cyclosporine-A, sirolimus and prednisone
        iii. Prednisone/CNI free arm: sirolimus, reduced dose CsA with prednisone withdrawn at day 5 and CsA converted to MPA at 6 months
    b. The prednisone/CNI-free group achieved similar 2-year graft survival to the triple therapy group. Improved mean GFR was shown in the prednisone/CNI-free group at 24 months ($P<0.05$). Mean fasting blood glucose similar between arms.
    c. Data from this study demonstrate that low-immune responder SPK patients achieved similar graft survivals at 2-years with prednisone/CNI free maintenance regimen. These patients also had an improved renal profile.

L. Malheiro J, Martins L, Fonseca I, et al. Steroid withdrawal in simultaneous pancreas-kidney transplantation: a 7-year report. *Transplant Proc*. 2009 Apr; 41(3):909-12. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19376386.
    a. Report of a retrospective review of 77 SPK patients from May 2000 to December 2007 who received thymoglobulin induction therapy and tacrolimus and mycophenolate mofetil maintenance therapy with a late steroid withdrawal protocol.
    b. Complete steroid withdraw by 1 year was accomplished in 77.8% of patients who had at least one year of follow-up and no case of acute rejection occurred in these patients.

c. Patient and graft survival was similar to other international SPK transplant units.
    i. Patient, kidney, and pancreas survival at 1 year were 93%, 91% and 86% respectively.
    ii. Eleven patients developed acute rejection. Patients demonstrated low prevalence of hypertension, hyperlipidemia, and obesity.
d. Results of this study reflect safety of steroid withdrawal without increase in immune related events.

M. Peixoto EM, Froud T, Gomes LS, et al. Effect of exenatide on gastric emptying and graft survival in islet allograft recipients. *Transplant Proc*. 2011;43(9):3231-4. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22099764.
    a. Report of a prospective study in 10 patients examining long-term use (up to 4 years) of exenatide in islet transplantation to examine the effect on gastric emptying and graft survival.
    b. Eight out of the ten patients were able to tolerate the study intervention for 48 months. Approximately 63% of patients discontinued the study drug due to nausea over 4 years.
    c. Data from this study demonstrate that exenatide treatment suppressed abnormal glucagon response, delayed average time to glucose peak, and prolonged graft survival. However, the more acute effects of exenatide use were not maintained once the medication was discontinued.

N. Qi M, Kinzer K, Danielson KK, et al. Five-year follow-up of patients with type 1 diabetes transplanted with allogeneic islets: the UIC experience. *Acta Diabetol*. 2014;51(5):833-43. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25034311.
    a. Report of a five-year, single-center, open label, prospective phase I/2 follow up outcomes in 10 islet cell transplants at the University of Illinois Hospital and Health Sciences Center.
        i. Four patients went through the Edmonton protocol while the other six received the Edmonton protocol in combination with exenatide and etanercept. *NOTE:* Intended immunosuppression regimen for Edmonton protocol was sirolimus and tacrolimus.
    b. All 10 patients achieved insulin independence after 1-3 transplants. Overall, 60% of patients remained insulin independent at five years. Most patients achieved hemoglobin A1c < 6.0%.
    c. Data from this single center experience demonstrate long-term insulin independence with thymoglobulin induction in additional to Edmonton protocol.

O. Rajab A, Pelletier RP, Ferguson RM, et al. Steroid-free maintenance immunosuppression with rapamune and low-dose neoral in pancreas transplant recipients. *Transplantation*. 2007 Nov 15;84(9):1131-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17998868.
    a. Report of a retrospective, single-center review of new steroid free pancreas transplant protocol implementation.
    b. Between August 2003 and May 2006 steroid free pancreas transplants (n=97) were compared to all pancreas transplants performed prior to new protocol initiation who received maintenance steroid immunosuppression (n=124).
        i. Induction of thymoglobulin

ii. Maintenance therapy of rapamycin and reduced dose cyclosporine, and prednisone for first 5 days
iii. Previous protocol of maintenance of cyclosporine and MMF with steroid

c. One-year patient and graft survival were comparable between groups. There was a lower incidence of acute rejection in the steroid-free arm 9.3% compared to 28.3% in steroid arm (P<0.01) but no difference in mean serum glucose or creatinine levels between the two groups at one year.
d. Data from this single center experience demonstrate excellent graft survival with significantly reduced acute rejection incidence via steroid-free maintenance therapy with CsA and rapamycin.

P. Sageshima J, Ciancia G, Chen L, et al. Everolimus with low-dose tacrolimus in simultaneous pancreas and kidney transplantation. *Clin Transplant*. 2014;28(7):797-801. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24779669.
   a. Report of a retrospective analysis of 23 SPK recipients at a single center from November 2011 to March 2013 evaluating safety and efficacy of everolimus compared to mycophenolate sodium in SPK transplants.
      i. All patients received dual induction with basiliximab and thymoglobulin and low-dose tacrolimus plus corticosteroids.
      ii. Everolimus arm: n=9
      iii. Mycophenolate sodium arm: n=14
   b. Median follow-up of 14 month: pancreas graft survival was 100% in both arms, however renal graft survival was 100% and 93% in everolimus and mycophenolate sodium arms respectively. No episodes of rejection were observed.
   c. There were no significant differences in surgical complications, hemoglobin A1c, or serum creatinine.
   d. Data from this analysis demonstrates comparable short-term outcomes with everolimus and mycophenolate sodium in combination with FK/steroids and dual induction.

Q. Shapiro AM, Ricordi C, Hering BJ, et al. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med.* 2006; 355: 1318–1330. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/17005949.
   a. Report of a single group, multicenter study of outcomes in islet cell transplantation utilizing Edmonton Protocol to explore the feasibility and reproducibility of islet transplantation.
   b. Nine international sites enrolled a total of 36 subjects with type 1 diabetes mellitus who underwent islet transplantation from pancreases of deceases donors. Transplantation occurred within 2 hours of purification.
      i. Immunosuppression: five doses of daclizumab 1mg/kg over 8 weeks, sirolimus once daily to level of 12-15 ng/mL for 3 months then 7-12 ng/mL, tacrolimus twice daily to level of 3-6 ng/mL.
   c. At 1 year, 44% had insulin independence with adequate glycemic control, 28% has partial function, and 20% complete graft loss.
      i. A total of 58% achieved insulin independence at any point in the trial.
         - At 2 years, 76% of these patients required insulin again.

ii. Of the patients who achieved insulin independence at 1 year, 31% remained independent at 2 years.

d. Data from this trial demonstrate that islet transplantation utilizing the Edmonton Protocol can restore endogenous insulin production and provide stability in blood glucose levels; however, insulin independence on average lasted 2 years post-transplant.

R. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med*. 2000;343:230-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10911004.

a. Introduction of Edmonton Protocol for islet cell transplantation.

b. Seven patients with type 1 diabetes and history of sever hypoglycemia and metabolic instability who underwent islet transplantation with daclizumab induction and maintenance regimen of sirolimus and tacrolimus were evaluated.

i. All patients achieved insulin independence in a mean follow up of 11.9 months; all patients required islets from two donor pancreases.

ii. Mean glycosylated hemoglobin were normal post-transplant.

c. Observation form this registry data demonstrate that islet transplant in type 1 diabetic patients can lead to insulin independence with metabolic control in a steroid-free immunosuppression regimen.

S. Stegall MD, Simon M, Wachs ME, et al. Mycophenolate mofetil decreases rejection in simultaneous pancreas-kidney transplantation when combined with tacrolimus or cyclosporine. *Transplantation*. 1997 Dec 27;64(12):1695-700. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9422404.

a. Report of a single center, prospective, randomized study evaluating acute rejection rates and morbidity in SPK transplant recipients when mycophenolate mofetil was added to maintenance regimen.

b. Induction with OKT3 and prednisone (tapered to 5 mg/day by month 6).

i. Tacrolimus and mycophenolate mofetil n=18

ii. Cyclosporine (Neoral) and mycophenolate mofetil n=18

iii. Compared to historical group (n=18) of conventional cyclosporine (Sandimmune) and azathioprine

c. Rates for biopsy proven acute rejection were significantly lower with FK+MMF and CsA+MMF (11% each) compared CsA+AZA historical group (77%, $p<0.01$). No significant difference in infection rates or metabolic control.

d. Data from this study show that MMF treatment significantly decreases incidence of biopsy proven acute rejection in SPK patient compared to AZA in historical group.

T. Tekin Z, Garfinkel MR, Chon WJ, et al. Outcomes of pancreatic islet allotransplantation using the Edmonton Protocol at the University of Chicago. *Transplant Direct*. 2016 Sep 13;2(10):e105. eCollection 2016 Oct. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27795987.

a. Report of long-term follow up of patients who underwent pancreatic islet cell transplantation under the Edmonton Protocol.

i. Nine subjects were followed for 10 years after initial islet transplant who received up to 3 separate islet infusion.

ii. Induction therapy was interleukin 2 receptor antibody with maintenance regimen of sirolimus and tacrolimus.

b. Of the 9 patients, 5 dropped out in early phase (50% due to noncompliance resulting in poor islet function). The 4 remaining patients remained insulin free for cumulative time of 5 years after first transplant.

c. Results from this report demonstrate durable long-term insulin-free diabetes control with islet transplant in patients with brittle diabetes.

U. Vessal G, Wiland AM, Philosophe B, et al. Early steroid withdrawal in solitary pancreas transplantation results in equivalent graft and patient survival compared with maintenance steroid therapy. *Clin Transplant*. 2007 Jul-Aug; 21(4):491-7. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/17645708.

a. Report of a retrospective, single-center evaluation of early steroid withdrawal in solitary pancreas transplants between January 2001 and December 2003.

i. Induction with thymoglobulin followed by tacrolimus and mycophenolate mofetil in both arms

ii. Historical arm: maintained steroid (n=32)

iii. Study arm: steroid withdrawal at 21 days post-transplant (n=22)

b. Early corticosteroid withdrawal in solitary pancreas transplant resulted in fewer infections (p=0.04) and no increased risk of rejection or graft loss at 1 year.

i. One-year rejection: historical 27.3% vs study 37.5% (p=NS)

ii. Pancreas graft survival: historical 95.5% vs study 81.3% (p=NS)

iii. Patient survival: historical 100% vs study 93.8% (p=NS)

c. Data form this single center study demonstrate early steroid withdrawal in isolated pancreas transplant (either alone or after kidney transplant) can be achieved without increased rejection or graft loss rates during the first year.

2.3. Desensitization therapy

Search terms: pancreas transplant AND desensitization, pancreas transplant AND sensitization, pancreas transplant AND plasmapheresis, pancreas transplant AND rituximab

A. Heilman RL et al. Outcomes of simultaneous kidney-pancreas transplantation with positive crossmatch. *Transplantation Proceedings.* 2009:41: 303-306. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19249540.
   a. Studied 72 consecutive simultaneous pancreas kidney transplant (SPKT) recipients
      i. Study group: 14 patients with positive pretransplant cross-matches (positive CDC-B cell and/or positive flow T or B cross-match)
         1. Induction with low dose intravenous immunoglobulin (IVIg), rabbit antithymocyte globulin (rATG; total dose 6 mg/kg), or alemtuzumab (30 mg single dose) and maintenance with tacrolimus, mycophenolate mofetil (MMF), and corticosteroids
      ii. Control group: 58 SPKT recipients with a negative crossmatch
         1. Induction with rabbit antithymocyte globulin (rATG; total dose 6 mg/kg), or alemtuzumab (30 mg single dose) and maintenance with tacrolimus, mycophenolate mofetil (MMF), and steroid avoidance
   b. Biopsy proven acute rejection occurred more often in the study patients (50%) than the control patients (10%)
   c. Graft survival at 18 months was similar between the groups (76.9% in the study group, 89.6% in the control group)

B. Kykalos S et al. Successful simultaneous pancreas-kidney re-transplant in a highly human leukocyte antigen-sensitized patient. *Transplantation Proceedings.* 2017:49: 1652-1655. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/28838458
   a. Single patient case report of a 45 year old female with a SPK in 2004 secondary to juvenile diabetes mellitus type I. Transplantation was complicated by rejection and loss of organ function for both organs in 2009. Highly sensitized (PRA >85%) (sensitization events include pregnancy, previous transplant, multiple transfusions).
   b. Desensitization Protocol:
      i. Rituximab 375 mg/$m^2$ (max 650 mg) x1 dose
      ii. Plasmapheresis + IVIG x5 doses every 14 days
      iii. Total 8 cycles of IVIG/Plasmapheresis required for negative cross-match to be achieved.
   c. Successful re-transplantation of SPK in 2013, with good early graft function. Patient experienced borderline cellular rejection (BANFF 97 classification) and was successfully treated with 3 day steroid pulse.

D. Mattiazzi AD et al. Highly sensitized patients: Miami transplant institute experience. *Clinical Transplant.* 2014:171-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26281142.
   a. Studied allograft failure in 45 highly sensitized patients (RTX and SPK)
      i. Study group: n = 35 received induction IS w/ rATG, basiliximab, and methylprednisolone with rituximab ± IVIG ± plasmaspheres
      ii. Control group: n= 10 induction w/ rATG, basiliximab, and methylprednisolone
   b. The cumulative proportion of patients who remain free of death or allograft failure was significantly higher in the Rituximab (87%) versus the Control group (60%) (p = 0.047).

2.4. Diagnosis and Management of rejection

Search terms: pancreas transplant AND rejection, ("Pancreas Transplantation"[Mesh]) AND ( "Graft Rejection/diagnosis"[Mesh] OR "Graft Rejection/therapy"[Mesh] )

A. De Kort H, Mallat MJ, van Kooten C, et al. Diagnosis of early pancreas graft failure via antibody-medicated rejection: single-center experience with 256 pancreas transplantations. *Am J Transplant.* 2014 Apr;14(4):936-42. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24712331
    a. Retrospective review of 256 SKP between 1985-2010 at one center. A total of 33 SPKs lost their pancreas graft <1 year after transplant. AMR was diagnosed in 7 cases, 8 cases were suspicious for AMR and 18 cases were not due to AMR. All patients with acute AMR of the pancreas lost their renal grafts <1 year after transplant.
    b. Histopathological analysis of early pancreas graft loss is advisable to rule out the possibility of AMR, particularly because a diagnosis of acute AMR has important consequences for renal graft outcomes.
B. Dong M, Parsaik AK, Kremers W, et al. Acute pancreas allograft rejection is associated with increased risk of graft failure in pancreas transplantation. *Am J Transplant*. 2013 Apr;13(4):1019-1025.Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23432918.
    a. Retrospective review of 227 consecutive pancreas transplants performed at one center from 1998 to 2009. Treatment of rejection included corticosteroid boluses along with either OKT3 (5 mg/day for 7- 10 days) or ATG (1.5 mg/kg/day for 5-10 days).
    b. Incidence of partial or complete loss was low due to treatment of acute rejection, however, acute rejection, especially within the first 3 months, was associated with an increased risk of long-term complete loss. Acute rejection within the first year was associated with an increased risk of at least partial loss.
C. Drachenberg CB, Torrealba JR, Nankivell BJ, et al. Guidelines for the diagnosis of antibody-mediated rejection in pancreas allografts-updated Banff grading schema. *Am J Transplant*. 2011 Sep;11(9):1792-802. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21812920
    a. Comprehensive guidelines for the diagnosis of AMR, best identified by a combination of serological and immunohistopathological findings consisting of
        i. Identification of circulating donor-specific antibodies, and histopathological data including
        ii. Morphological evidence of microvascular tissue injury
        iii. C4d staining in interacinar capillaries
    b. Acute AMR is diagnosed conclusively if these three elements are present, whereas a diagnosis of suspicious for AMR is rendered if only two elements are identified. The identification of only one diagnostic element is not sufficient for the diagnosis of AMR but should prompt heightened clinical vigilance. AMR and ACMR may coexist, and should be recognized and graded independently.
D. Loupy A, Haas M, Solez K, et al. The Banff 2015 Kidney Meeting Report: Current Challenges in Rejection Classification and Prospects for Adopting Molecular Pathology. *Am J Transplant*. 2017 Jan;17(1):28-41. Retrieved from http://onlinelibrary.wiley.com/doi/10.1111/ajt.14107/full.

    a. Updated Banff pancreas allograft rejection grading schema located in table 7 (page 38-39)

E. Redfield RR, Rickels MR, Naji A, Odorico JS. Pancreas Transplantation in the Modern Era. *Gastroenterol Clin North Am*. 2016 Mar;45(1):145-66. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26895686
    a. Review of current indications, patient selection, surgical considerations, complications, and outcomes in the modern era of pancreas transplantation.
    b. Includes rejection diagnosis and treatment algorithm (pages 156-160, table 6).

F. Redfield RR, Kaufman DB, Odorico JS, et al. Diagnosis and Treatment of Pancreas Rejection. *Curr Transplant Rep*. 2015;2(2):169-175. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26000231.
    a. Review of the diagnosis and treatment of pancreas rejection. Rejection treatment algorithm from the University of Wisconsin.

G. Salahuddin S, Astor B, Parajuli S, Djamali A, Odorico J, Mandelbrot D. Outcomes with Steroids Alone for Biopsy-Proven Pancreas Transplant Rejection. [abstract]. *Am J Transplant*. 2016; 16 (suppl 3). Retrieved from https://atcmeetingabstracts.com/abstract/outcomes-with-steroids-alone-for-biopsy-proven-pancreas-transplant-rejection/
    a. Retrospective review of 42 pancreas transplant recipients from January 1997 to December 2013 who had biopsy proven rejection and were treated with steroid pulse alone.
    b. Patients with grade 1 pancreas transplant rejection can be treated with steroids alone (62% responded to treatment), where grade 2 and 3 rejection rarely responded to steroids alone (14% responded) and was associated with higher graft failure rates.

2.5. Graft failure/retransplantation

Search words: pancreas AND retransplantation

A. Andres A, Livingstone S, Kin T, et al. Islet-after-failed-pancreas and pancreas-after-failed islet transplantation: Two complementary rescue strategies to control diabetes. *Islets*. 2015;7(6):e1126036. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26854597.
    a. Report of single-center outcomes associated with pancreas transplant after failed islet transplant (n=2), and islet transplant after failed pancreas transplant (n=3).
    b. Metabolic control was favorable in PAI with both patients insulin independent. In the IAP, one patient achieved insulin independence after two islet infusions. Of note, average wait time was 4.5 years for PAI and 0.35 years for IAP.
    c. Data from this single center experience demonstrate both strategies to be feasible, however more robust data is warranted. PAI outcomes may be offset due to duration of waitlist time secondary to sensitized patient status.
B. Buron F, Thaunat O, Demuylder-Mischler S, et al. Pancreas retransplantation: a second chance for diabetic patients? *Transplantation*. 2013 Jan 27;95(2):347-52. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23222920.
    a. Study aiming to evaluate pancreas retransplantation outcomes in type 1 diabetic patients with end stage renal disease who have lost their primary graft.
    b. Comparison of pancreas retransplanted patients (n=17) graft and patient survival at 1 and 5 years versus whole pancreas transplantation population (n=569)
    c. Pancreas retransplanted patient graft survival was similar to primary graft survival of the whole population (71% vs. 79% at 1 year and 59% vs. 69% at 5 years; P=0.5075) and statistically better than first pancreas survival (71% vs. 29% at 1 year and 59% vs. 7% at 5 years; P=0.0008) regardless of cause of graft loss.
    d. Results of this report demonstrate pancreas retransplantation as a safe procedure with acceptable graft survival that should be proposed to diabetic patients who have lost their primary graft.
C. Gasteiger S, Cardini B, Göbel G, et al. Outcomes of pancreas retransplantion in patients with pancreas graft failure. *Br J Surg*. 2018 Dec;105(13):1816-1824. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30007018.
    a. Report of a retrospective observational study of pancreas retransplant (PRT) at a single center between 1997 and 2013.
    b. A total of 52 patients were identified as PRTs and median follow up was 65 months. Graft survival at 1 year and 5 years were 79% and 69% respectively, with patient survival rates of 96% and 89%.
        i. Graft loss was defined as return to insulin dependence with incidence of 42% in the 65 month follow up period.
        ii. Though not statistically significant, 5 year graft survival was better after SPK retransplantion than PRT alone: 80% vs 63%, p=0.266.
    c. Results of this single center experience demonstrate PRT as an option for patients with primary pancreas transplant failure.

D. Gerber PA, Hochuli M, Benediktsdottir BD, et al. Islet transplantation as safe and efficacious method to restore glycemic control and to avoid severe hypoglycemia after donor organ failure in pancreas transplantation. *Clin Transplant*. 2018 Jan;32(1). Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29140547.
    a. Report of single center experience assessing safety and efficacy of islet transplant after initial pancreas transplant with subsequent organ failure.
        i. Islet arm: Islet after pancreas organ failure (n=10)
        ii. Pancreas arm: pancreas retransplant after pancreas organ failure (n=3)
        iii. Control arm: pancreas graft failure without islet transplant (n=7)
    b. Ten patients received islet transplant after pancreas organ failure and were followed for 51 months.
        i. Primary end point of hemoglobin A1c < 7% and freedom from severe hypoglycemia was achieved by 9/10 IAP, 3/3 PRT, and 0/7 control group.
        ii. Insulin requirement decreased by 50% in IAP arm.
    c. Results from this single center experience support IAP after deceased donor pancreas graft failure as an option to improve glycemic control and reduce hypoglycemia events.
E. LaMattina JC, Sollinger HW, Becker YT, Mezrich JD, Pirsch JD, Odorico JS. Simultaneous pancreas and kidney (SPK) retransplantation in prior SPK recipients. *Clin Transplant*. 2012 May-Jun;26(3):495-501. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22032238.
    a. Report of a retrospective review summarizing outcomes of repeat SPK in prior SPK recipients (n = 9) from a cohort of over 1200 SPK recipients.
    b. Median time to retransplant was 7.8 years. Retransplant pancreatic allograft survival was 78% at one year and 67% at two years.
        i. Overall renal allograft survival was 89% at one year and 78% at two years.
        ii. Patient survival was 100% at both one and three years.
    c. Data from this review support acceptable survival of repeat SPK allografts despite increased technical and immunologic demands of retransplantation. As 89% of patients underwent transplant nephrectomy and 78% underwent transplant pancreatectomy, a graftectomy prior to or at the time of retransplantation may be necessary.
F. Perosa M, Sergi F, Noujaim H, et al. Outcomes after pancreas retransplantation: is the juice worth the squeeze? *Curr Opin Organ Transplant*. 2018 Aug;23(4):461-466. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29979264.
    a. Review of current literature outlining outcomes of pancreas retransplantation as compared to primary pancreas transplant.
    b. Overall, a lower graft survival of PRTs is reported compared to primary pancreas transplantations. This finding could be due to differences in transplant category: primary pancreas transplantations are predominantly SPKs, which are known to have superior graft survival outcomes over solitary pancreas transplantations.
    c. Graft loss due to technical reasons are similar between primary pancreas transplant and PRTs, however PRT has shown to have a greater occurrence of surgical complications.
    d. This review demonstrates that PRT may be a valid and effective option for select patients at an experienced center.
G. Seal J, Selzner M, Laurence J, et al. Outcomes of pancreas retransplantation after simultaneous kidney-pancreas transplantation are comparable to pancreas after kidney transplantation alone.

*Transplantation*. 2015 Mar;99(3):623-8. Retrieved from https://www-ncbi-nlm-nih-gov/pubmed/25148379.

a. Report of retrospective analysis evaluating short- and long-term outcomes for recipients of pancreas retransplant after primary pancreas after kidney transplantation.
b. Between 2003 and 2012, 96 pancreas only transplants performed: primary PAK (n=78) and PRT (n=18).
c. Pancreas graft survival similar between arms: PAK 88.2% vs PRT 100% at 1 year and PAK 85.1% vs PRT 85.1% at 3 year. At three years, both groups had comparable hemoglobin A1c, serum creatinine, and oral glucose tolerance tests.
d. Results of this analysis demonstrate pancreas retransplantation as a safe and efficacious option as it was associated with similar postoperative complication risks and similar graft survival compared to primary PAK.

H. Siskind E, Maloney C, Jayaschandaran V, et al. Pancreatic retransplantation is associated with poor allograft survival: an update of the United Network for Organ Sharing database. *Pancreas*. 2015 Jul;44(5):769-72. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25931257.

a. Report evaluating the outcomes of pancreas retransplant compared to primary pancreas transplant based on the data from the United Network for Organ Sharing database.
b. Adult patients who received either a pancreas transplant or kidney-pancreas transplant between 1996 and 2012 were identified.
    i. Retransplant arm: n=1149
    ii. Primary transplant arm: n=19705
c. Analysis of patient survival was superior for PRT arm ($p<0.0001$) while graft survival was superior in primary transplant arm ($p<0.0001$).
d. Results from this analysis demonstrate a lower graft survival than previous studies, partially due to predominance of PAT versus SPK. Further studies are needed to determine true impact of PRT and identify specific patients who would benefit most.

2.6. Diabetes secondary to chronic pancreatitis or cystic fibrosis without pancreatectomy

Search words: pancreatogenic diabetes; diabetes AND cystic fibrosis

A. Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol*. 2013;19(42):7276-81. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/24259958.
   a. Review and discussion of the prevalence, diagnosis, and treatment of diabetes in chronic pancreatitis

B. Ballman M, Hubert D, Assael BM, et al. Repaglinide versus insulin for newly diagnosed diabetes in patients with cystic fibrosis: a multicentre, open-label, randomized trial. *The Lancet Diabetes & Endocrinology*. 2018;6(2): 114-121. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29199116
   a. Multicenter, open-label, randomized trial of 75 patients comparing insulin with repaglinide therapy for patients with newly diagnosed cystic fibrosis-related diabetes
   b. Results of the study showed no significant difference in the change in Hemoglobin-A1c, blood glucose concentration, FEV1, or FVC at 12 months or 24 months.
   c. Change in BMI z-score differed significantly at 12 months but not 24 months.

C. Kayani K, Mohammed R, Mohiaddin H. Cystic-fibrosis related diabetes. *Front Endocrinol*. 2018;9: 1-11. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29515516
   a. Review and discussion of the pathophysiology, complications, diagnosis, and management of cystic-fibrosis related diabetes mellitus.

D. Lek N, Acerini CL. Cystic fibrosis related diabetes mellitus - diagnostic and management challenges. *Curr Diabetes Rev*. 2010;6(1):9-16. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/20034372.
   a. Review and discussion of the diagnosis and treatment of cystic fibrosis related to diabetes mellitus

E. Mohan K, Israel KL, Miller H, et al. Long-Term Effect of Insulin Treatment in cystic fibrosis-related diabetes. *Respiration*. 2008; 76: 181-186. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/17960051
   a. Retrospective, single-center, longitudinal cohort study of 42 patients with cystic fibrosis-related diabetes to determine the long-term impact (3 years) of insulin treatment on patients with cystic fibrosis-related diabetes
   b. Results showed significant improvement in FEV1, FVC and BMI at one year; however, the effect was only sustained at three years for BMI. FEV1 and FVC were not significantly different at 2 and 3 years after insulin initiation.

F. Moran A, Brunzell C, Katz M, 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. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/21115772
   a. Clinical guidelines for the management of cystic fibrosis related diabetes mellitus

G. Onady GM, Stolfi A. Insulin and oral agents for managing cystic fibrosis-related diabetes. *Cochrane Database Syst Rev*. 2013;7:CD004730. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23893261
   a. Systematic review to determine the efficacy of various insulin formulations and repaglinide in the management of diabetes in cystic fibrosis patients
   b. Outcomes evaluated included blood sugar control, pulmonary function, nutritional status, infectious complications, quality of life, and mortality

H. Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatology*. 2013;13(4):336-42. Retrieved from: http://www.ncbi.nlm.nih.gov/pubmed/23890130

a. Working group recommendations and review of the medical problems, diagnostic methods and treatment options for chronic pancreatitis-associated diabetes from a consensus meeting in 2012

I. Wynne K, Devereaux B, Dornhorst A. Diabetes of the exocrine pancreas. *Journal of Gastroenterology and Hepatology*. 2018;34(2):346-354. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/30151918

a. Review and discussion of the related etiologies, pathophysiology, screening, diagnosis, and treatment for diabetes of the exocrine pancreas

J. Yoon, C. Evolving mechanistic views and emerging therapeutic strategies for cystic fibrosis-related diabetes. *Journal of the Endocrine Society*. 2017;1(11):1386-1400. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/29264462

a. Review and discussion of the pathophysiology, risk factors, and management of cystic fibrosis-related diabetes.

2.7. Pancreatectomy Prior to Pancreas Transplant

Search words: total pancreatectomy, autotransplantation, pancreas transplant

A. Colling KP, Bellin MD, Schwarzenberg SJ, et al. Total pancreatectomy with intraportal islet autotransplantation as a treatment of chronic pancreatitis in patients with CFTR mutations. *Pancreas*. 2018 Feb;47(2):238-244. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29206667.
    a. Single center outcomes comparison of total pancreatectomy with islet autotransplantation in patients with CFTR mutation associated chronic pancreatitis to those without CFTR mutation.
    b. Retrospective review between 2002 and 2014 identified 20 CFTR homozygotes, 19 CFTR heterozygotes, and 20 matched controlled without CFTR mutations.
        i. Postoperative glycosylated hemoglobin and c-peptide levels were similar between groups.
        ii. At 1 year, 40% of CFTR homozygotes, 22% of CFTR heterozygotes, and 35% of control patients were insulin independent.
    c. Data from this single center experience convey similar outcomes for CFTR patients compared to those with chronic pancreatitis from other etiologies.
B. Gruessner RW, Sutherland DE, Drangstveit MB, et al. Pancreas allotransplants in patients with a previous total pancreatectomy for chronic pancreatitis. *J Am Coll Surg*. 2008 Mar;206(3):458-65. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/18308216.
    a. Report of a single center experience of pancreas allotransplants with a previous total pancreatectomy for chronic pancreatitis.
    b. Between June 1, 1986 and May 15, 2007, the center performed 26 pancreas allotransplants in 18 patients who had previous total pancreatectomy for chronic pancreatitis.
        i. Pancreas graft survival at 1 and 3 years for CSA were 67% and 50%, for tacrolimus 73% and 51%, and CNI-free at 1 year was 40% (p=0.13).
        ii. Mean episodes of rejection for CSA was 2.1, tacrolimus was 1.4, and CNI-free was 0.6.
        iii. Patient survival at 1 and 3 years for CSA and tacrolimus were 100% and 100% while CNI-free at 1 year was 40%.
    c. Data from this series of pancreas allotransplants showed graft survival rates of more than 70% with a tacrolimus-based immunosuppression regimen. Additionally, pancreas transplant demonstrated success in treating both endocrine and exocrine insufficiency.
C. Gruessner RW, Sutherland DE, Dunn DL, et al. Transplant options for patients undergoing total pancreatectomy for chronic pancreatitis. *J Am Coll Surg*. 2004 Apr;198(4):559-67; discussion 568-9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15051008.
    a. Report of a single center experience with islet autotransplants at the time of, or with pancreas allotransplants after total pancreatectomy.
    b. Between February 1, 1977 and June 30, 2003, the center performed 112 islet autotransplant at the time of total pancreatectomy and 20 pancreas allotransplants in 13 patients who previously had total pancreatectomy.

i. Islet autotransplant at the time of total pancreatectomy was associated with high islet yield with 70% of patients achieving complete insulin independence.
ii. Patients with previously pancreatectomy of drainage resulted in low islet yield in 75%, complete insulin independence in less than 20%.
iii. Transplant related mortality at 1 year and 3 years was not impacted by pancreas allotransplant after total pancreatectomy.
iv. Pancreas graft survival at 1 year was 77% with tacrolimus-based immunosuppression compared to 67% with cyclosporine.

c. Data from this center supports pancreas allotransplant without transplant related mortality with tacrolimus-based immunosuppression.

D. Sutherland DE, Radosevich DM, Bellin MD, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. *J Am Coll Surg*. 2012 Apr; 214(4):409-24; discussion 424-6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/22397977.

a. Report of a more than 30-year single center series of 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet autotransplant.
b. Patient survival at 1 and 5 years was 96% and 98% in adults, 89% and 98% in children.
i. Islet autotransplant was defined as c-peptide greater than 0.6 ng/mL and achieved in 90% of patients.
ii. At 3 years, 30% of patients were insulin independent and 33% had partial function. Mean hemoglobin A1c was less than 7.0% in 82% of patients.
iii. By 2 years post-transplant, 59% of patient ceased all narcotics.
c. Data from this series support that total pancreatectomy and islet autotransplant can improve quality of life in refractory chronic pancreatitis. Additionally, islet autotransplant preserves islet function in most patients with insulin independence in 25% of adults.

E. Walsh RM, Saavedra JR, Lentz G, et al. Improved quality of life following total pancreatectomy and autoislet transplantation for chronic pancreatitis. *J Gastrointest Surg*. 2012 Aug;16(8):1469-77. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22673773.

a. Single center experience for impact of total pancreatectomy with islet autotransplant for treatment of chronic pancreatitis on quality of life.
b. Total of 20 patients from 2007 and 2010 were retrospectively assessed using pre- and post-operative depression anxiety stress scale, pain disability index, and visual analogue pain scale. Median follow up was 12 months.
i. Pre-operatively, 45% reported moderate pain while 55% reported severe pain.
ii. Post-operatively, 80% reported no or mild abdominal pain ($p<0.001$). However, only 30% patients ceased narcotics.
iii. Pain disability index improved from 79% preoperatively to 90% postoperatively ($p=0.002$).
iv. Up to 60% and 70% demonstrated improvement in depression and anxiety respectively ($p=0.033$).
c. Data from this report demonstrate improvement in pain and quality of life in patients with chronic pancreatitis who underwent total pancreatectomy with islet autotransplant. Of note, greatest improvement was seen in patients without prior pancreatic surgery, younger aged, and higher level of preoperative pain.

F. Webb MA, Illouz SC, Pollard CA, et al. Islet auto transplantation following total pancreatectomy: a long-term assessment of graft function. *Pancreas*. 2008 Oct;37(3):282-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/18815550.
    a. Report of a single center series of 46 patients having undergone simultaneous total pancreatectomy with immediate islet autotransplant.
    b. At 10 years of follow up, 12 patients had shown periods of insulin dependence for a median of 16.5 months and 5 patients remained insulin dependent.
        i. Notable increase in insulin requirement per kilogram per day during follow up.
        ii. All of the patients were c-peptide positive at most recent assessment with high fasting and stimulated c-peptide values during follow up: average of 1.44 ng/mL and 2.86 ng/mL respectively.
    c. Data from this series demonstrate that though there is a notable decline in islet function after autotransplant, evidence of long-term insulin secretion exists.

2.8. Exocrine Drainage in Pancreas Transplant

Search terms: pancreas AND exocrine drain, pancreas AND enteric, pancreas AND bladder

A. Adamec M, Janousek L, Lipár K, et al. A prospective comparison of bladder versus enteric drainage in vascularized pancreas transplantation. *Transplant Proc*. 2004;36(4):1093-4. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15194380.
    a. Prospective, randomized, single center study of 40 pancreas transplant recipients comparing bladder versus enteric drainage between October 1999 and January 2002
    b. No difference in length of hospital stay, patient survival, graft survival, rejection, or infection rates.
    c. Increase incidence of dehydration, metabolic acidosis, and urologic complications in patients who received a bladder-drained pancreas.
B. Corry RJ, Chakrabarti P, Shapiro R, Jordan ML, Scantlebury VP, Vivas CA. Comparison of enteric versus bladder drainage in pancreas transplantation. *Transplant Proc*. 2001 Feb-Mar;33(1-2):1647-51. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11267454.
    a. Prospective, single-center trial of 243 patients transplanted (simultaneous kidney-pancreas, pancreas after kidney, and pancreas alone transplants) between July 1994 and April 2000
    b. Overall survival was higher in the enteric drained group; however, survival was higher in the bladder drained group in the solitary pancreas patients. No difference was seen in the SKPT group. Survival rates were also lower with cold ischemia times greater than 20 hours compared to less than 15 hours.
    c. Complication rates, including relaparotomy and anastomotic bleeding requiring transfusion in were higher in the bladder drained group.
C. Jiménez-Romero C, Manrique A, Meneu JC, et al. Comparative study of bladder versus enteric drainage in pancreas transplantation. *Transplant Proc*. 2009 Jul-Aug;41(6):2466-8. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19715953.
    a. Single center, retrospective study of 118 patients undergoing SPK or PAK who were transplanted between March 1995 to September 2008 who were managed with either enteric or bladder drainage
    b. Higher rates of graft thrombosis and urinary tract infections were identified in the bladder drained group compared with the enteric-drained group. There was no significant difference in the incidence of graft loss between the two groups.
    c. Three-year patient and graft survival were not different between the two groups.
D. Lo A, Stratta RJ, Hathaway DK, et al. Long-term outcomes in simultaneous kidney-pancreas transplant recipients with portal-enteric versus systemic-bladder drainage. *Transplant Proc*. 2001 Feb-Mar;33(1-2):1684-6. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11267468.
    a. Retrospective, single-center analysis of 78 SKPT patients transplanted between January 1990 and January 1996 managed with either portal-enteric or systemic-bladder drainage
    b. There were no differences in kidney and pancreas survival rates at 5 years; however, there was significantly higher kidney graft survival in the portal-enteric group at 10 years. There was no difference in patient survival at any time point.

    c. There was a non-significant trend toward improved patient and graft survival, less metabolic complications, morbidity and better quality of life in the portal-enteric drainage group.

E. Senaratne NV, Norris JM. Bladder vs enteric drainage following pancreatic transplantation: How best to support graft survival? A best evidence topic. *Int J Surg*. 2015 Oct;22:149-52. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26343973.
    a. Best evidence topic that reviewed four retrospective cohort studies that compare enteric and bladder exocrine drainage.
    b. The authors concluded that graft survival at 1 year is comparable between the two methods of exocrine drainage.

F. Siskind E, Amodu LI, Pinto S, et al. Bladder Versus Enteric Drainage of Exocrine Secretions in Pancreas Transplantation: A Retrospective Analysis of the United Network for Organ Sharing Database. *Pancreas*. 2018 May/Jun;47(5):625-630 . Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/29683972.
    a. Retrospective analysis of UNOS data composed of 19,934 pancreas and kidney-pancreas transplant recipients transplanted between 1996 and 2012 comparing patients who received transplants with enteric drainage with Roux-en-Y, enteric drainage without Roux-en-Y, and bladder drainage.
    b. Unadjusted results showed improved patient and graft survival with enteric drainage without Roux-en-Y compared with enteric drainage with Roux-en-Y and bladder drainage consistent up to 15 years after transplant.

D. Stratta RJ, Gaber AO, Shokouh-amiri MH, et al. A prospective comparison of systemic-bladder versus portal-enteric drainage in vascularized pancreas transplantation. *Surgery*. 2000;127(2):217-26. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/10686988.
    a. A prospective, single center study of 32 pancreas transplants from 1997 to 1998 randomized to receive systemic anastomosis with bladder drain or portal anastomosis with enteric drain.
    b. Patient survival, graft loss, hospital length of stay, and overall infectious complications were similar between groups at a mean follow-up time point of 8 months.
    c. There was a non-statistically significant increase in number of readmissions, and urinary tract infections and a statistically significant increase in metabolic acidosis, and dehydration in the patients who received a bladder drained pancreas.

2.9. Systemic versus Portal Venous Anastomosis

Search terms: pancreas AND portal vein, pancreas AND vascular anastomosis, pancreas AND systemic vein

A. Bazerbachi F, Selzner M, Marquez MA, et al. Portal venous versus systemic venous drainage of pancreas grafts: impact on long-term results. *Am J Transplant*. 2012;12(1):226-32. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22054257.
   a. Retrospective, single center study of 192 SPK transplant recipients between November 1995 to November 2007 who received either portal or systemic venous drainage
   b. No difference between groups in regards to patient or allograft survival, or kidney function at 1, 5, 7, and 10 years post-transplant

B. Oliver JB, Beidas AK, Bongu A, Brown L, Shapiro ME. A comparison of long-term outcomes of portal versus systemic venous drainage in pancreatic transplantation: a systematic review and meta-analysis. *Clin Transplant.* 2015;29(10):882-92. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26172035.
   a. Systematic review and meta-analyses of 15 studies published regarding systemic versus portal vein drainage between 1989 and 2014
   b. No difference in fasting blood glucose levels, hemoglobin A1c, or C-peptide were seen. No difference was seen between lipid panels in either group.
   c. No meta-analysis could be performed on rejection, complications or patient or graft survival.

C. Philosophe BP, Farney AC, Schweitzer EJ, et al. Superiority of portal venous drainage over systemic venous drainage in pancreas transplantation. *Ann. Surg.* 2001;234(5):689-696. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11685034
   a. Prospective, single center study of 117 simultaneous kidney and pancreas transplant recipients between August 1995 and June 2000 who received either systemic venous enteric or portal venous enteric drainage
   b. Overall 36-month patient survival was similar between groups
   c. Thirty-six-month graft survival was higher and rejection rates were lower in the portal venous drainage group

2.10. Anastomosis leak or thrombosis post-pancreas transplantation

Search terms: pancreas AND thrombosis, pancreas AND heparin, pancreas AND octreotide

A. Aboalsamh G, Anderson P, Al-abbassi A, Mcalister V, Luke PP, Sener A. Heparin infusion in simultaneous pancreas and kidney transplantation reduces graft thrombosis and improves graft survival. *Clin Transplant*. 2016;30(9):1002-9. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/27293140.
    a. A retrospective cohort analysis of 62 SPK recipients from 2004 to 2014 of patients randomized to low-dose aspirin versus unfractionated heparin infusion immediately post-transplant in addition to low-dose aspirin started on post-op day 5
    b. There was a statistically significant increase in graft survival and decrease in graft thrombosis in the heparin infusion group; however, there was no difference in patient survival up to 5 years after transplant.
    c. No difference was seen in the rate of postoperative anastomotic leak or hemorrhage.
B. Benedetti E, Coady NT, Asolati M, et al. A prospective randomized clinical trial of perioperative treatment with octreotide in pancreas transplantation. *Am J Surg*. 1998;175(1):14-7. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/9445231.
    a. A prospective, randomized, open label trial at a single center of 17 bladder-drained pancreas transplants. The study compared patients who received octreotide 100 mcg subcutaneously every 8 hours for 5 days post-transplant to those who received no additional therapy.
    b. There was significantly less technical complications, including pancreatitis, anastomotic leaks and intra-abdominal infections, in the group that received octreotide.
C. Farney AC, Rogers J, Stratta RJ. Pancreas graft thrombosis: causes, prevention, diagnosis, and intervention. *Curr Opin Organ Transplant*. 2012;17:87–92. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/22186095.
    a. Review of the diagnosis, prevention, and management of pancreas graft thrombosis
        i. Management focuses on the efficacy of various agents including aspirin, unfractionated and low molecular weight heparin, and warfarin
D. Hesse UJ, Meester D, Troisi R, Cathenis K, Lameire N, Hemptinne B. The use of low dose octreotide prophylaxis in pancreatic transplants with enteric drainage. Results of a prospective randomized single center trial. *Clin Transplant*. 2005;19(3):299-303. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/15877788.
    a. Prospective, randomized, open label study evaluating the use of octreotide 100 mcg every 8 hours for 7 days in 40 pancreas transplant recipients compared to no medical intervention
    b. There was no statistically significant difference in the rates of complication post-transplant (hemorrhage, fistula formulation at the anastomotic site, pancreatitis, thrombosis) or patient and graft survival. There was a trend towards better graft survival in patients who did not receive octreotide. There was no difference in the amount of urinary amylase or lipase secreted.

E. Scheffert JL, Taber DJ, Pilch NA, Chavin KD, Baliga PK, Bratton CF. Clinical outcomes associated with the early postoperative use of heparin in pancreas transplantation. *Transplantation*. 2014;97(6):681-5. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24285337.
    a. A retrospective, single-center analysis of 152 pancreas transplant recipients from 2001 to 2009.
    b. Fifty-two patients received a heparin infusion (no specified dosing or target partial thromboplastin time). The other 100 patients received a 300 mg aspirin suppository starting on post-operative day 1 and eventually were switched to aspirin 325 mg orally daily as tolerated.
    c. The study showed no difference in overall thrombosis rates, bleeding rates, patient survival, or graft survival between groups. There was a trend towards more partial thrombosis with heparin infusion and higher rates of exploratory laparotomy; however, there was also a trend towards higher rates of graft survival and lower rates of graft loss due to thrombosis in heparin treated patients.
F. Schenker P, Vonend O, Ertas N, et al. Incidence of pancreas graft thrombosis using low-molecular-weight heparin. *Clin Transplant*. 2009;23: 407-414. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/19537302.
    a. Single-center, retrospective review of 188 pancreas transplant recipients who received low-dose IV heparin adjusted to aPTT compared to those who received once daily low molecular weight heparin at prophylactic doses.
    b. There was no difference in the rate of graft thrombosis (after adjusting for confounding) or major bleeding; however, the rate of graft loss and graft loss due to thrombosis was significantly higher in the unfractionated heparin group.