2. Pancreas and islet cell transplantation

2.1 Induction therapy

2.1.1 Pancreas transplant induction therapy

2.1.2 Islet cell transplant induction therapy

2.2 Maintenance therapy

2.3 Desensitization therapy

2.4 Diagnosis and management of rejection

2.5 Graft failure/retransplantation

2.6 Diabetes secondary to chronic pancreatitis or cystic fibrosis without pancreatectomy

2.7 Pancreatectomy prior to pancreas transplant and/or islet autotransplant

2.8 Exocrine drainage in pancreas transplant

2.9 Systemic versus portal venous anastomosis

2.10 Anastomosis leak, thrombosis, or bleed post-pancreas transplantation

2.11 Management of complications following pancreas transplantation/miscellaneous

2.1. Induction therapy

2.1.1 Pancreas transplant induction therapy


- Literature review of current practice and developments in immunosuppressive regimens in pancreas transplantation. Induction used in ~90% with Tcell depleting induction ~90% of the time. Initial enthusiasm with steroid-free maintenance regimens however now mostly still steroid-maintenance along with tac/mmf. MTOri introduced later ~10% of the time, mostly due to CNI side effects.


- Retrospective analysis of long-term results of a randomized controlled trial comparing alemtuzumab induction plus tacrolimus monotherapy to antithymocyte globulin induction plus tacrolimus, mycophenolate mofetil, and steroids followed by individualized long-term immunosuppression in 30 SPK patients between 2006 and 2010. 5- year and 9-year pancreas graft, renal graft, and patient survival were similar between groups.


- Retrospective study of 166 PTX who received induction with rabbit antithymocyte globulin +/- rituximab and maintenance therapy with tacrolimus, sirolimus, and mycophenolate mofetil.

- 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. 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.


- 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). 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.


- Retrospective study of thymoglobulin vs basiliximab induction in SPK transplant recipients between February 2000 and August 2013 at a single center. 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.


- 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. 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.


- Retrospective study of thymoglobulin vs basiliximab induction in SPK transplant recipients between January 2001 and August 2008 at a single center. 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.
2.1.2 Islet cell transplant induction therapy


- Retrospective chart review of pre-transplant evaluation, allocation, and 1-year clinical outcomes of patients with Type 1 diabetes undergoing beta-cell replacement therapy (either pancreas transplant alone (PTA) or islet cell transplant (ITX)) at a national transplant center in Norway.
Evaluation for transplant candidacy by a multidisciplinary team was associated with a significant reduction in referral of patients compared to prior evaluation by a single nephrologist (84% vs. 40%; \(<0.005\)

- Review article of current practice, benefits, and challenges associated with insulin therapy, pancreas transplant, and islet cell transplant in the management of patients with diabetes mellitus

- Prospective, multi-center, open-label study of patients undergoing islet cell transplantation from 2002 to 2008. Patients received one of four possible induction regimens. 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.

- 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. 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

- Review article summarizing immunosuppression strategies for simultaneous solid organ transplantation recipients published between 1/1/2010 and 5/1/2020. Includes a focus on induction and maintenance immunosuppression practices in simultaneous pancreas kidney (SPK) transplantation and impact on patient survival.

- Single-center, open-label, prospective, randomized study in SPK recipients randomized to a tacrolimus or sirolimus based immunosuppressive regimen. Data from this study showed noninferiority of SRL compared to TAC when introduced at 3 months after SPK with regard to graft survival. Results do not favor SRL use as cornerstone therapy after SPK given high rates of discontinuation.

- Single-center, open-label randomized trial comparing pancreas graft survival in in SPK transplant recipients receiving sirolimus or MMF in combination with tacrolimus and early steroid withdrawal.
Data from this study demonstrate that sirolimus in combination with tacrolimus is an effective maintenance regimen in SPK transplant recipients.

- Long-term infectious and noninfectious outcomes of 179 pancreas transplant recipients treated with alemtuzumab induction and maintenance therapy (EAE (extended alemtuzumab exposure) to minimize CNI and/or steroids) vs. 159 pancreas transplant patients with standard induction and maintenance therapy.

- 490 SPK, 45 PAK pt. 13 switched to mtor-i from either CNI or MMF due to side effects (mostly CMV or GI intolerance) at ~11 months post-txp. ~13% discontinuation rate in the MTORi group (proteinuria, pharmacodermia), clinical complications included kidney and pancreas graft dysfunction; however, low acute rejection rates. 20% graft loss over 15 years attributed to chronic allograft dysfunction.

- Multicenter, open-label, phase II, randomized study comparing belatacept-based immunosuppressive regimen to a CNI-based regimen in SPK recipients. Results of this study did not provide sufficient evidence to prevent pancreas rejection in SPK patients receiving belatacept while undergoing CNI withdrawal.

- Single-center, retrospective study of SPK recipients between June 2014 and October 2018. Data from this study show that LCPT is a safe, effective method of administering tacrolimus in pancreas transplant patients.

- Data was analyzed from UNOS database for adult pancreas and SPK transplant recipients between 1987 and 2016. Data from this analysis showed improved allograft survival and early patient survival with the use of mTORi for immunosuppression following pancreas transplant.

- Multicenter, prospective study comparing rapamycin pre-treatment before islet transplant (n=13) to no rapamycin pre-treatment (n=28). Data from this study suggest that rapamycin pre-treatment before islet transplantation succeeds in reducing insulin requirements before and after transplantation.
Sirolimus was the cornerstone of islet cell txp maintenance at the turn of the century when it was used in 80% of regiments however this has now decreased to 50%. For pancreas txp, use of mtor-I has decreased from 20% to 10%. Decreased use of mtor-I likely due to side effects and lack of better outcomes however remains a valuable second-line agent.


- Single-center, retrospective study of SPK recipients between December 2009 and June 2015 converted from TAC/MMF into TAC/mTOR immunosuppression. In this study, conversion from MMF to an mTOR inhibitor with a reduction in TAC dosing provided more effective prophylaxis against both CMV and BK viral replication than standard immunosuppression with TAC/MMF without compromising graft survival and acute rejection rates.


- Report of rat model evaluation of SGLT-2 inhibitor empagliflozin on tacrolimus induced diabetes mellitus. 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.


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


- 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. 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.

- 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. Data from this single center experience demonstrate long-term insulin independence with thymoglobulin induction in additional to Edmonton protocol.


- 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. Data from this analysis demonstrates comparable short-term outcomes with everolimus and mycophenolate sodium in combination with FK/steroids and dual induction.


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


- 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. Results from this single center experience demonstrate that rapamycin combination with FK was better tolerated with more effective antirejection profile than MMF.


- 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. 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.


- 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). 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.

- 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. Results of this study reflect safety of steroid withdrawal without increase in immune related events.

- Report of a prospective study in 16 islet cell transplant recipients given exenatide for allograft dysfunction causing a new insulin requirement post-islet transplantation. 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.

- 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. 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.

- Report of a retrospective, single-center review of new steroid free pancreas transplant protocol implementation. 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.

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

- 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. 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.


- 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. 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 posttransplant.


- 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. 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.


- Report of an open-label, multicenter study comparing efficacy and safety of tacrolimus with microemulsion cyclosporine in patients who received SPK transplantation. 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. Data from this study demonstrate support for FK therapy in patients undergoing SPK due to type 1 diabetes with end-stage renal disease.


- Introduction of Edmonton Protocol for islet cell transplantation. Observation from 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.


- 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. 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.

2.3 Desensitization therapy

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%). Desensitization Protocol: Rituximab 375 mg/m² (max 650 mg) x1 dose, plasmapheresis + IVIG x5 doses every 14 days.


Studied allograft failure in 45 highly sensitized patients (RTX and SPK). 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).


Study group: 14 patients with positive pretransplant cross-matches (positive CDC- B cell and/or positive flow T or B cross-match). 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.

Control group: 58 SPKT recipients with a negative crossmatch. 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.

2.4. Diagnosis and management of rejection


Use of thymoglobulin for steroid-resistant acute rejection in 2 SPK patients who had recovered from COVID-19 but still with viral shedding
- Patient #1 had mild COVID-19 without reduction in IMS, rejection diagnosed based on lipase elevation and imaging, which did not improve after steroids. Did improve after thymoglobulin.
- Patient #2 with asymptomatic COVID-19, elevated Scr and new DSA. ACR plus chronic active AMR. Scr did not respond to PP/IVIG/rituximab/thymoglobulin, but he did not become symptomatic from COVID-19.


Comparison of HLA incompatibility scores of various algorithms to predict de novo DSA development and impact on graft survival in simultaneous pancreas-kidney transplant recipients
- Female sex and race were found to be significantly associated with development of de novo DSA post-transplant. De novo DSA development was associated with AMR and worse graft outcomes.

- Pre-transplant and de-novo DSA both associated with increased risk for AMR. Pancreas allograft biopsy essential for differentiating between ACR and AMR and guiding therapy for both PTA and also SPK and biopsy findings have found to be discordant. Treatment of rejection can prolong graft survival.


- Single-center retrospective review of 158 pancreas recipients treated for first episode of BPAR comparing response rate and long-term outcomes with steroids alone versus steroids plus ATG.
- 65 patients were treated with steroids alone; 83% of patients with grade I BPAR, 60% with grade II, and 33% with grade III responded to steroids alone. 93 patients were treated with steroids plus ATG; response rates were 69% in grade I, 76% in grade II, and 73% in grade III. Response rates and graft survival were not different with grade I rejection treated with either option, however, response rates and graft survival were significantly better with grade III rejection treated with the addition of ATG, and graft survival rates were significantly better with grade II rejection treated with the addition of ATG.


- Updated Banff pancreas allograft rejection grading schema located in table 7 (page 3839)


- Review of current indications, patient selection, surgical considerations, complications, and outcomes in the modern era of pancreas transplantation.
- Includes rejection diagnosis and treatment algorithm (pages 156-160, table 6).


- 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.
- 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.


- Review of the diagnosis and treatment of pancreas rejection. Rejection treatment algorithm from the University of Wisconsin.


- 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.
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.


- 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).
- 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.


- Comprehensive guidelines for the diagnosis of AMR, best identified by a combination of serological and immunohistopathological findings consisting of identification of circulating donor-specific antibodies, and histopathological data
- 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.

2.5. Graft failure/retransplantation


- Australian and New Zealand registry data from 2006-2016 used to build a model to compare survival between SPK and DDRT with dialysis in terms of life years saved and quality-adjusted life years.
- SPK best treatment for those under age 50 with ESRD and type 1 DM. For those over age 50 and ineligible for SPK, DDRT offers survival benefit over dialysis.


- Retrospective, single-center study of patients undergoing retransplantation (kidney or pancreas) receiving induction with alemtuzumab or rabbit antithymocyte-globulin from January 2001 and December 2016. Both groups received alemtuzumab induction for their primary transplant.
- There was no difference in 1 year rejection rates but use of alemtuzumab induction for retransplantation was associated with a significantly higher incidence of fungal infections compared to rabbit antithymocyte-globulin.
- Single-center cohort study of SPK recipients transplanted between 01/01/2000 and 12/31/2016 who experienced pancreas graft failure and retained kidney graft function. Patients were divided into groups that underwent pancreas retransplant and those who didn’t.
- At last follow-up, 60% of the repeat pancreas graft has failed, with a mean graft survival among failed pancreas grafts of 2.6 years. Uncensored and death censored kidney graft failure was significantly lower in the retransplant group (44% vs. 67% and 24% vs. 67%, respectively).

- 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%. Though not statistically significant, 5 year graft survival was better after SPK retransplantation than PRT alone: 80% vs 63%, p=0.266.
- Results of this single center experience demonstrate PRT as an option for patients with primary pancreas transplant failure.

- Ten patients received islet transplant after pancreas organ failure and were followed for 51 months. 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. Insulin requirement decreased by 50% in IAP arm.
- 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.

- Review of current literature outlining outcomes of pancreas retransplantation as compared to primary pancreas transplant.
- 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.

- Report of single-center outcomes associated with pancreas transplant after failed islet transplant (n=2), and islet transplant after failed pancreas transplant (n=3).
- 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.

- 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. 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.


- Report evaluating the outcomes of pancreas retransplant compared to primary pancreas transplant based on the data from the United Network for Organ Sharing database.
- Analysis of patient survival was superior for PRT arm (p<0.0001) while graft survival was superior in primary transplant arm (p<0.0001).
- 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.


- Study aiming to evaluate pancreas retransplantation outcomes in type 1 diabetic patients with end stage renal disease who have lost their primary graft.
- 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.
- 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.


- Retrospective review summarizing outcomes of repeat SPK in prior SPK recipients (n = 9) from a cohort of over 1200 SPK recipients.
- Median time to retransplant was 7.8 years. Retransplant pancreatic allograft survival was 78% at one year and 67% at two years.
- 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.

### 2.6. Diabetes secondary to chronic pancreatitis or cystic fibrosis without pancreatectomy
- Updated systematic review determining the efficacy of insulin and oral agents for the management of diabetes in cystic fibrosis patients
- Outcomes evaluated include blood sugar control, pulmonary function, nutritional status, microvascular and macrovascular disease complications, complications, and mortality
- No conclusive evidence for superiority of one agent over another in controlling hyperglycemia or clinical outcomes associated with cystic fibrosis related diabetes

- Review and discussion of medical treatment options for patients with cystic fibrosis related diabetes

- Multicenter, open-label, randomized trial of 75 patients comparing insulin with repaglinide therapy for patients with newly diagnosed cystic fibrosis-related diabetes
- 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.

- Review and discussion of the pathophysiology, complications, diagnosis, and management of cystic-fibrosis related diabetes mellitus.

- Updated clinical guidelines for the management of cystic fibrosis related diabetes mellitus

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

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

- Review and discussion of the prevalence, diagnosis, and treatment of diabetes in chronic pancreatitis
- 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

- Review and discussion of the diagnosis and treatment of cystic fibrosis related to diabetes mellitus.

- 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
- 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.

2.7. Pancreatectomy prior to pancreas transplant and/or islet autotransplant

- Single center retrospective review of 88 patients undergoing total pancreatectomy with islet autotransplantation (TPIAT) and the impact of pre-surgical body composition on islet function and sensitivity. Half of these chronic pancreatitis patients were overweight/obese; underweight was uncommon. Preoperative body weight and composition were associated with islet function but not insulin independence after TPIAT.

- Single center retrospective review of 25 patients that underwent left extended pancreatectomy (>60%) and islet autotransplant for a neoplasm located in the pancreatic neck or proximal body.
- There were no deaths and low morbidity. Patient and insulin-independent survival rates at 4 years were 100% and 96%, respectively. Glucose homeostasis remained within a nondiabetic range at all times for 19 (73%) of 25 patients. Patients undergoing islet autotransplant had a longer diabetes-free survival than did patients without islet autotransplant.
- In conclusion, islet autotransplant after extended pancreatic resection for neoplasms is a safe and successful procedure for preventing diabetes

- Single center observational study of 742 patients who underwent a total pancreatectomy and intraportal islet cell autotransplant (TPIAT), 215 who have 10 year follow-up data, to determine long-term durability TPIAT
- 10-year actuarial survival rate was 72% with BMI >30 kg/m² predicting 10-year mortality. Patient relief rates were 82% at 10 years and 90% at 15 years. 10-year insulin independence rate was 20% and partial graft function rate 32%. Dual procedure produced durable pain relief and sustained islet graft function, even post 10 years postoperatively.

- Single center retrospective review of 8 patients that underwent total pancreatectomy and pancreas transplant between 6/1/2005 and 7/1/2006.
- Patient survival rate at 1 and 3 years was 88% with death-censored graft survival of 100% and 86%, respectively. 75% remained insulin-free until their time of death, loss of follow-up or present day with 75% of these patients maintaining exocrine function without pancreatic enzyme supplementation.

- Single center outcomes comparison of total pancreatectomy with islet autotransplantation in patients with CFTR mutation associated chronic pancreatitis to those without CFTR mutation.
- At 1 year, 40% of CFTR homozygotes, 22% of CFTR heterozygotes, and 35% of control patients were insulin independent.
- Data from this single center experience convey similar outcomes for CFTR patients compared to those with chronic pancreatitis from other etiologies.

- Single-center retrospective review of the outcomes of 20 pediatric patients who underwent TPIAT.
- Mean age 13, 95% had chronic pancreatitis and 1 had acute recurrent pancreatitis alone. 90 days postoperatively vs. preoperatively there were significantly fewer patients receiving parenteral nutrition (0% vs 25%) and opioids (45% and 75%). Short Form 36-Item Health Survey scores also significantly improved. Insulin requirement decreased from 0.5 u/kg/d to 0.4 u/kg/d between discharge and 90 days. TPIAT is an effective option when debilitating disease persists despite maximal medical and endoscopic therapy.

- Case report of islet transplantation utilizing islet cells of the pancreas allograft which needed to be explanted due to bleed. 3 month outcomes show glycemic control, with some use of basal insulin.

- Report of a single center experience of pancreas allotransplants with a previous total pancreatectomy for chronic pancreatitis.
- 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).
- 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.


- Single-center retrospective review of women who had previously undergone TPIAT and subsequently completed pregnancies.
- 5 patients completed 7 total pregnancies with median time to conception of 21 months. 80% had increased exogenous insulin requirements; however compared to controls, no significant HbA1c, insulin use, or graft function differences were found at time of last follow-up. Long-term graft function was comparable between patients with a pregnancy after TPIAT and their matched controls, supporting the conclusion that pregnancy did not have a negative impact on graft function in women with a history of TPIAT.


- Report of a more than 30-year single center series of 409 patients with chronic pancreatitis who underwent total pancreatectomy and islet autotransplant.
- Patient survival at 1 and 5 years was 96% and 98% in adults, 89% and 98% in children.
- 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.


- Single center experience for impact of total pancreatectomy with islet autotransplant for treatment of chronic pancreatitis on quality of life.
- Pain disability index improved from 79% preoperatively to 90% postoperatively (p=0.002). Up to 60% and 70% demonstrated improvement in depression and anxiety respectively (p=0.033).
- 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.


- Report of a single center series of 46 patients having undergone simultaneous total pancreatectomy with immediate islet autotransplant.
- 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. 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.
- Data from this series demonstrate that though there is a notable decline in islet function after autotransplant, evidence of long-term insulin secretion exists.

- Report of a single center experience with islet autotransplants at the time of, or with pancreas allotransplants after total pancreatectomy.
- Transplant related mortality at 1 year and 3 years was not impacted by pancreas allotransplant after total pancreatectomy. Pancreas graft survival at 1 year was 77% with tacrolimus-based immunosuppression compared to 67% with cyclosporine.
- Data from this center supports pancreas allotransplant without transplant related mortality with tacrolimus-based immunosuppression.

2.8. Exocrine drainage in pancreas transplant


- Single-center retrospective review comparing post-operative complications and infections in 83 pancreas transplant recipients with intra-operative prophylactic drain placement vs. no drain placement.
- Enteric drainage was utilized in all grafts and 30/83 (36%) of patients had at least one prophylactic drain placed. Prophylactic abdominal drain placement following pancreas transplant was associated with a lower incidence of need for reoperation for peripancreatic infections, but no difference in peripancreatic infections or graft survival.


- Retrospective, single center study of 593 pancreas transplant patients with bladder-drained pancreata. Patients who underwent enteric conversion were compared to those who did not.
- Enteric conversion was associated with an increased risk of acute rejection but was not associated with a higher rate of graft loss or mortality.


- Retrospective, single center study of first-time SPK transplants with bladder drainage performed between 1985 and 2000. Patients who underwent enteric conversion were compared to those who did not.
- Enteric conversion was not associated with a difference in pancreas or kidney graft survival.


- Retrospective review of bladder-drained (BD) and enteric-drained (ED) pancreas transplant patients for UTI and urine was analyzed for pH and host defense proteins/peptides (HDPs) which increase susceptibility to UTIs.
- In-vitro analysis showed decreased growth of Ecoli in an alkaline pH and increased growth with the addition of pancreatin (pancreatic digestive enzyme). In the presence of HDP there was significant ecoli killing however not with the addition of pancreatin.

- 1999 to 2015, 318 pancreas transplants, 180 of which had bladder-drained transplants. Of the 180, 82 had enteric conversion at ~20 months post-txp and the remainder did not.
- Graft survival rate significantly higher for the enteric-converted group for 10 years compared to those that remained with bladder drainage.


- 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.


- Best evidence topic that reviewed four retrospective cohort studies that compare enteric and bladder exocrine drainage. The authors concluded that graft survival at 1 year is comparable between the two methods of exocrine drainage.


- 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
- 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. Three-year patient and graft survival were not different between the two groups.


- Prospective, randomized, single center study of 40 pancreas transplant recipients comparing bladder versus enteric drainage between October 1999 and January 2002
- No difference in length of hospital stay, patient survival, graft survival, rejection, or infection rates. Increase incidence of dehydration, metabolic acidosis, and urologic complications in patients who received a bladder-drained pancreas.

Prospective, single-center trial of 243 patients transplanted (simultaneous kidney pancreas, pancreas after kidney, and pancreas alone transplants) between July 1994 and April 2000

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. Complication rates, including relaparotomy and anastomotic bleeding requiring transfusion were higher in the bladder drained group.


Retrospective, single-center analysis of 78 SKPT patients transplanted between January 1990 and January 1996 managed with either portal-enteric or systemic-bladder drainage

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. 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.


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.

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. 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


Retrospective database review of UNOS data on adults receiving pancreas and SPK transplants from 1987-2016 were analyzed

No significant difference in graft or patient survival at 1,3,5,10 or 15-years between groups. In a subgroup analysis of patients undergoing pancreas after kidney transplant, portal venous drainage was associated with a reduced risk of death compared to systemic venous drainage


Systematic review and meta-analyses of 15 studies published regarding systemic versus portal vein drainage between 1989 and 2014

No difference in fasting blood glucose levels, hemoglobin A1c, or C-peptide were seen. No difference was seen between lipid panels in either group.

• Retrospective, single center study of 192 SPK transplant recipients between November 1995 to November 2007 who received either portal or systemic venous drainage.
• No difference between groups in regards to patient or allograft survival, or kidney function at 1, 5, 7, and 10 years post-transplant.


• 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
• Overall 36-month patient survival was similar between groups. Thirty-six-month graft survival was higher and rejection rates were lower in the portal venous drainage group.

2.10. Anastomosis leak, thrombosis, or bleed post-pancreas transplantation

• Retrospective review of 26 patients receiving a heparin-based protocol and 37 patients received D40 protocol
• Patients in the D40 group had similar thrombosis rates but were less likely to have had graft loss as a result of thrombosis or substantial postoperative bleeding. Those who received D40 had significantly lower CRP and WCC on days 2, 3, and 7.

• Retrospective evaluation of 384 pancreas transplantations and postoperative plasma C-peptide, adjusted C-peptide, and blood sugar levels
• Difference of aCP was significant during the first week after transplantation between patients with thrombosis and those with functional allograft: 63.2 vs 26.7 on day 1, p=0.0003; 61.4 vs 26.7 on day 3, p<0.0001; 64.8 vs 5.7 on day 7, p <0.0001, respectively. Glycemia had a median increase of 8% on the day of failure, whereas C-peptide and aCP had respectively a median decrease of 88% and 83%.

• Single center retrospective analysis of 235 simultaneous pancreas-kidney transplants
• Managed with watchful waiting and imaging (9, 12%), therapeutic anticoagulation (12, 29%), laparotomy and graft thrombectomy (4, 10%). 16 required pancreatectomy (6.8%).
• Risk of thrombosis leading to graft loss was 11.2- fold higher in recipients with a BMI >25 (OR 11.2; 95% CI, 1.1-116.7; p=0.043).

• Retrospective study of 177 pancreas transplant recipients
• 318 computed tomography (CT) images were evaluated for pancreas allograft thrombosis (PAT) using the Cambridge pancreas allograft thrombosis (CPAT) grading system. Inter-rater
agreement expressed in the Fleiss’ kappa, within clinically relevant thrombosis categories was 0.626 for Grade 2 and 0.781 for Grade 3 venous thrombosis.


- Single center retrospective analysis of early intestinal complications and relation to vascular events
- 337 patients examined, 23 patients had early intestinal complications (including intestinal obstruction, paralytic ileus, intestinal fistula without anastomotic dehiscence, ischemic graft duodenum, dehiscence of a duodenoojejunostomy, and anastomotic dehiscence in jejunum after pancreas transplantectomy). Of intestinal complications, 4 were associated with vascular thrombosis, with 2 graft losses.


- Retrospective cohort study of adult SOT CMV-seronegative patients who received allograft from a seropositive donor or a seronegative donor
- Assessed impact of CMV exposure at transplantation on the rate of posttransplant thrombotic events. A CMV D+/R- transplantation was independently associated with an increased risk of a thrombotic event over 5 years (adjusted hazard ratio, 3.027; 95% confidence interval, 1.669-5.488).


- Many reported post-operative complications after pancreas transplant are early complications however there is growing attention for late complications after pancreas transplant.
- Case series of 3 SPK (2 enteric-drained and 1 bladder-drained) with anastomotic bleed over 10 years from transplant (of 122 total SPK in the same time period, 1992-2018).


- Systematic review of the risk factors for early pancreatic allograft thrombosis following SPK transplant. Included 63 studies (39 cohort studies, 22 conference abstracts, and 2 meta-analyses)
- 1,127 thrombi were identified in 15,936 deceased donor, whole pancreas transplants, conferring a 7.07% overall thrombosis rate. Thrombosis resulted in pancreatic allograft loss in 83.3% of reported cases. This review has established significant associations between donor and recipient characteristics, procurement and preservation methodology, transplantation technique, postoperative management, and increased risk of early thrombosis in the pancreas allograft.


- Retrospective single center review of allograft thrombosis outcomes of four anticoagulation regimens (none, SQ heparin/aspriin, with or without dextran, and heparin infusion) administered to 95 SPKs or PTAs between 1/1/2015 and 11/202018.
Recipients with or without allograft thrombosis had similar recipient and graft survival, 95% and 86%, respectively. Outcomes of prophylaxis regimens correlated with intensity of anticoagulation (increased hemorrhagic complications with IV heparin compared to no anticoagulation; higher thrombosis in regimens lacking antiplatelet therapy).


- Single center retrospective review of the rate of portal vein thrombosis (PVT) based on pharmacologic prophylaxis protocol and impact of PVT on islet graft function after total pancreatectomy with islet autotransplantation from 2001 to 2008.
- 12 patients (6.6%) developed PVT, which resolved by 6 months after TPIAT in 10 patients. No significant difference in PVT rate between UFH and enoxaparin prophylaxis recipients, but higher thrombotic complications in enoxaparin group (6% vs 0%). No difference in islet function for patients that developed PVT versus those who did not.


- Single case report of a 34-year-old male with a 9 year history of type 1 diabetes mellitus with ESRD who underwent an SPK complicated by a sub-occlusive thrombus within the pancreatic transplant portal vein on POD1.
- Patient underwent catheter-directed thrombolysis and thrombectomy after which he received systemic anticoagulation with IV heparin 25,000 UI per 24 h. Patient was discharged 16 days after transplant with normal functioning pancreas.


- Guideline covers intra-abdominal infections across all organ transplants. Within pancreas transplant recipients, the duodenal anastomotic leaks can have catastrophic consequences as polymicrobial abscesses can lead to graft loss and death.


- There was evidence of partial thrombosis in 59 cases (26%), of which the majority was treated with heparin and a vitamin K antagonist with graft preservation in 57/59 patients (97%).


- 379 pancreas transplants from 2000-2016 analyzed, all enteric-drained. 5 patients (1.3%) developed late hemorrhagic episodes from the anastomosis (duodenojejunostomy). Clinical manifestations = decreased Hgb, hematochezia, hemodynamic instability.
- Treatment is challenging and includes endoscopy, interventional radiology, and surgery.

- 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
- 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. No difference was seen in the rate of postoperative anastomotic leak or hemorrhage.


- 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. 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.


- Review of the diagnosis, prevention, and management of pancreas graft thrombosis. Management focuses on the efficacy of various agents including aspirin, unfractionated and low molecular weight heparin, and warfarin.


- 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.
- 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.


- 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
- There was no statistically significant difference in the rates of complication posttransplant (hemorrhage, fistula formation 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.
- 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.
- There was significantly less technical complications, including pancreatitis, anastomotic leaks and intra-abdominal infections, in the group that received octreotide.

2.11 Management of complications following pancreas transplantation/miscellaneous

- Review describes the impact of diabetic gastroparesis and orthostatic hypotension in post-operative course of pancreas transplant patients and analyze various treatment modalities

- Retrospective study examining all UK solid organ pancreas transplants from 1994 – 2016 (n=1452)
- Multivariate analysis showed increasing recipient BMI had significant impact on graft survival (P=0.03, HR 1.04 [1.00-1.08]). Recipients on dialysis with a BMI >30 had a statistically significant decrease in both graft (P=0.002) and patient survival (P=0.015).

- Retrospective analysis of 164 simultaneous kidney-transplant recipients and their levels of first three-day plasma amylase, drain fluid amylase, C-reactive protein, C-peptide, plasma trypsinogen, and white blood cell count
- First-day plasma amylase had the best value in predicting complications. Cut off is 6 times the upper limit of normal.

- Letter to the editor describing the impact of COVID-19 on volume of kidney transplants
- Estimated decrease of 10% in volume of kidney transplants nationwide

- Prospective study in 123 pancreas transplant recipients examining glucose control profiles over the first 5 days postoperatively
- Glucose AUC was a significant predictor of graft failure during 3.6 years of follow up. Hyperglycemia predicted a 3-fold higher risk of graft failure [HR (95% confidence interval): 3.0 (1.1-8.0); P = .028].

- Case series describing chronic graft vs host disease occurring in recipients of pancreas after kidney transplantation
• Two case reports, one occurring at 5.5 months and 42 months after pancreas transplant. Management strategies suggested: increasing immunosuppression, plasma transfusion.