

Pancreas and Islet Cell Transplantation and Intestinal Transplantation



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Pancreas and Islet Cell Transplantation

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Disclosures

- Speaker's Bureau – Veloxis Pharmaceuticals (ended April 2021)

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Learning Objectives

- Demonstrate an understanding for common complications of pancreas transplantation and develop strategies to prevent or treat these complications.
- Devise a monitoring strategy to evaluate exocrine and endocrine function after pancreas transplantation.
- Compare and contrast the advantages and disadvantages of pancreas and islet cell transplantation.

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Pancreas Transplantation

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History and Background

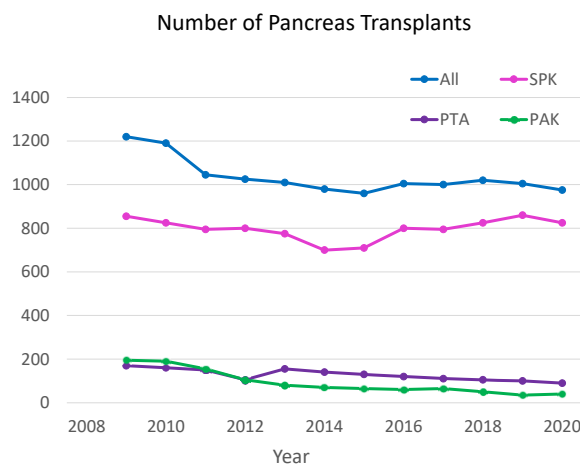
- First pancreas transplant at University of Minnesota in 1966
- Types of pancreas transplants
 - Simultaneous Kidney/Pancreas (SPK)
 - Pancreas Transplant Alone (PTA)
 - Pancreas after Kidney Transplant (PAK)

Surgery 1967;61:827-37

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Pancreas Transplant Trends

- Pancreas volumes decline in 2020
 - Onset of COVID-19 pandemic
 - Decreased referral and graft acceptance rates
- Majority male, ages 35-54
- Type 2 DM accounted for 21.3% of transplants
- Increase in Black, Asian and Hispanic recipients



Am J Transplant 2022;22(S2):137-203

Br J Surg 2021;108:e109-e110

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Indications for Pancreas Transplant

- Type 1 Diabetes Mellitus
- Type 2 Diabetes Mellitus
 - C-peptide >2 ng/mL and BMI <30 kg/m²
- Severe pancreatic exocrine insufficiency
 - Pancreatectomy for chronic pancreatitis, pancreatic neoplasms, or trauma
 - Cystic fibrosis

Diabetes Care 2006;29:935

OPTN Policy 11: Allocation of Pancreas, Kidney-Pancreas, and Islets. Accessed 3/14/21

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Listing Criteria and Allocation

- Pancreas Registration
 - Diagnosis with diabetes
 - Have pancreas exocrine insufficiency
 - Requirement of procurement of transplantation of part of a multiple organ transplant for technical reasons
- Simultaneous Kidney-Pancreas Registration
 - Diabetes OR pancreatic exocrine insufficiency WITH
 - Renal insufficiency (GFR <20ml/min)
 - Insulin requirement for T2DM
- Allocation Prioritized
 - Time on waitlist
 - Zero A/B/DR antigen mismatch
 - cPRA \geq 80%
 - Distance between transplant center and donor hospital

OPTN Policy 11: Allocation of Pancreas, Kidney-Pancreas, and Islets. Accessed 3/23/22

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Definition of Graft Failure

- 2018 Definition
 - Graft pancreatectomy
 - Patient death
 - Recipient re-registers for a pancreas transplant
 - Recipient registers for an islet cell transplant after pancreas transplant
 - Total insulin use of 0.5 units/kg/day for 90 consecutive days after transplant
- Previously used definitions
 - Graft pancreatectomy
 - Patient death
 - Use of exogenous insulin
 - Fasting hyperglycemia

90 Day Graft Failure	SPK	PTA	PAK
2018	6.5%	6.1%	8.8%
2019	5.1%	5.2%	6.8%
2020	7.2%	6.5%	4.7%

OPTN Pancreas Transplant Committee Meeting Minutes 5/15/2019. Accessed 1/24/2021;

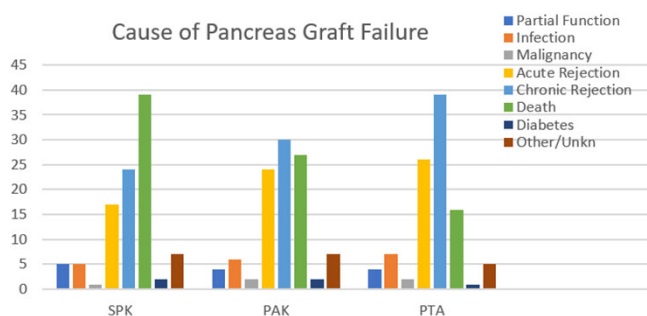
Am J Transplant 2022;22(S2):137-203

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Pancreas Transplant Outcomes

	SPK	PTA	PAK
Mortality – 1 year	2.6%	1.8%	3.5%
Mortality – 10 years	25.3%	20.1%	26.8%
Rejection - 1 year	10.6%	21.8%	12.5%

- Early graft failure
 - Technical graft failure
- Late graft failure
 - Acute and chronic rejection
 - Death with a functioning graft



Am J Transplant 2022;22(S2):137-203; Rev Diabet Stud 2016;13:35-58

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Immunological Risk

- Common Risk Factors
 - Retransplant
 - High PRA
 - Positive B-cell crossmatch
 - HLA mismatching
 - Black race
 - Young recipient age
 - CMV infection
 - Medication non-adherence
- Pancreas Specific Risk Factors
 - Diabetes
 - Erratic drug absorption from gastroparesis and enteropathy
 - Autoimmunity
 - Pancreas transplant alone
 - Unreliable markers of rejection
- Exocrine function rejects first
 - Elevated enzymes most common presentation

Expert Rev Clin Immunol 2014;10:117-132

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Monitoring

- Endocrine function
 - Serum glucose, hemoglobin A1c, C-peptide
- Exocrine function
 - Serum amylase, serum lipase, urinary amylase
- Autoantibodies
 - Anti-glutamic acid decarboxylase (GAD)
 - Islet cell antibodies (ICA)
 - Anti-tyrosine phosphatase (anti-IA2)
 - Anti-insulin antibodies

- Causes of elevated pancreatic enzymes

Early (<45 days)
Enzyme leak , Infected fluid/abscess, Thrombosis, Ileus, Acute rejection
Mid Postoperative (45 days – 1 year)
Acute rejection , SBO, Pseudocyst , Constipation, Abscess, CMV pancreatitis
Late (> 1 year)
Acute rejection , Chronic rejection , SBO/ventral hernia, Intrinsic pancreatic abnormality, native pancreatitis , CMV pancreatitis

Curr Transpl Rep 2015;2:169-75

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Surgical Procedure

- Endocrine Venous Drainage
 - Systemic Venous Drainage
 - Via IVC or external/common iliac arteries
 - Portal Venous Drainage
 - Via SMV then undergoes first-pass metabolism through the liver
 - No differences seen in function or long-term survival
 - Systemic venous drainage most common

- Exocrine Duct Drainage
 - Bladder Drainage
 - Urinary amylase to monitor for rejection
 - Complications – metabolic acidosis, cystitis, UTI, reflux pancreatitis
 - Enteric Drainage
 - Physiologic delivery of enzymes to intestine for reabsorption
 - Patient and graft survival similar
 - Enteric drain most common

Surg Clin N Am 2019;99:87-101

Rev Diabet Stud 2016;13:35-58

HPB 2019;21:195-203

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Complications – Graft Thrombosis

- Most common reason for early technical graft failure
 - SPK 4.1%, PAK 6.4%, PTA 5.0%
- Contributing factors
 - Hypoperfusion
 - Pancreatitis
 - Atherosclerosis
 - Enteric vs bladder drainage
 - Donor characteristics
- Early elevation in blood glucose and serum amylase
- Management
 - Pancreatectomy
 - Thrombectomy and anticoagulation
- Role of prophylaxis
 - Low dose aspirin
 - IV heparin
 - LMWH
 - Combination therapy

Rev Diabet Stud 2016;13:35-58

Surg Clin N Am 2019;99:87-101

Curr Opin Organ Transplant 2012;17:87-92

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Graft Thrombosis Prophylaxis Strategies

Aspirin alone vs. UFH + aspirin	UFH vs. LMWH
62 SPK <ul style="list-style-type: none"> • Aspirin alone (n=29): aspirin 81 mg on POD1 • UFH + aspirin (n=33): UFH POD0 500 IU/h, decreased by 100 IU/h QD + aspirin 81 mg on POD5 	173 SPK, 11 PAK, 4 PTA <ul style="list-style-type: none"> • UFH (n=129): 400-600IU/h, titrate to 2x normal aPTT x 9±4.9 days • LMWH (n=58): certoparin 3000 or nadroparin 3800 anti-factor Xa IU daily
Results: aspirin vs. UFH + aspirin <ul style="list-style-type: none"> • Graft Thrombosis <ul style="list-style-type: none"> • 7 (25.7%) vs 0 (0%), p=0.008 • Graft Survival <ul style="list-style-type: none"> • 78.8% vs 100%, p=0.009 • No difference in PRBCs, pancreatic leaks or hemorrhage 	Results: UFH vs. LMWH <ul style="list-style-type: none"> • Graft Thrombosis <ul style="list-style-type: none"> • 22 (17%) vs. 4 (7%), p=0.047 • 1-year Graft Survival <ul style="list-style-type: none"> • 74.4% vs. 89.6% • No difference in major bleeding requiring re-laparotomy

Clin Transplant 2016;30:1002-9

Clin Transplant 2009;23:407-14

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Graft Thrombosis Prophylaxis Strategies

LMWH + Aspirin

Kidney and SPK Transplants deemed at high risk of graft thrombosis

- Enoxaparin 1 mg/kg BID, n=2
- Enoxaparin 30 mg BID, n=11
- Aspirin 81 mg daily

Results in SPK population, n=3

- 1 major bleed
- No thrombotic complications

- Other strategies
 - Warfarin
 - Clopidogrel
 - DOAC
- Management Considerations
 - Antiplatelet vs. Anticoagulant

Pharmacotherapy 2002;22:184-7
Curr Opin Organ Transplant 2012;17:87-92

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Complications - Graft Pancreatitis

- 2nd most common complication

	Onset	Frequency	Presentation	Risk Factors	Management
Physiological Acute Graft Pancreatitis	30 min – 72 hrs after reperfusion	100%	<ul style="list-style-type: none"> • ↑ amylase, lipase in surgical drain • ↑ CRP 	<ul style="list-style-type: none"> • Cold ischemia time • Donor age • Microvascular disease of the graft 	<ul style="list-style-type: none"> • Avoid hypotension at reperfusion • Calcium channel blocker • Corticosteroids at procurement
Early Graft Pancreatitis Common cause of graft loss	0 – 3 months	35-38%	<ul style="list-style-type: none"> • Pain • ↑ amylase, lipase • Hematuria 	<ul style="list-style-type: none"> • Donor age > 50, DCD grafts • Hemodynamic instability • Portal venous, bladder exocrine drainage • Infection, thrombosis 	<ul style="list-style-type: none"> • Antithrombotic therapy • Bowel rest • TPN • Treatment of concurrent infections
Late Graft Pancreatitis Uncommon cause of graft loss	> 3 months	14-25%	<ul style="list-style-type: none"> • Pain • ↑ amylase, lipase, glucose • Fever, vomiting, diarrhea, hematuria 	<ul style="list-style-type: none"> • Bladder drainage • Graft trauma • Mechanical stricture, microvascular thrombosis • Recurrent infection, CMV • Occlusion of Sphincter of Oddi 	<ul style="list-style-type: none"> • Conservative – bowel rest, hydration, antibiotics • Surgical – percutaneous drainage, enteric conversion

Curr Opin Organ Transplant 2013;18:89-96

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Complications - Orthostatic Hypotension

- Incidence unknown
- Onset: Days to weeks post-transplant
- Reversible process with slow recovery
- Causes
 - Autonomic neuropathy
 - Polyuria in bladder drainage
 - Hyperinsulinemia in enteric drainage
 - Rapid glucose normalization
- Management
 - IV fluids, NaCl tablets, fludrocortisone, midodrine
- Midodrine for orthostatic hypotension
 - N=8 (7 SPK, 1 PTA)
 - 6 portal-enteric, 2 systemic-bladder
 - Initiated 3.1 mo (1 wk – 4 mo)
 - Mean initial dose 18 mg/day, max 30 mg/day

	Pre-midodrine	Post-midodrine
Change in BP, sit to stand	43 mmHg	27 mmHg
Fluid, L/day	1.8	1.3
Fludrocortisone, mg/d	0.2 mg	0.3 mg
Supine HTN meds	1.3	0.4

Exp Clin Transplant 2008;2:127-131

Transplant Direct 2021;7:e795; Clin Transplantation 2000;14:42-7

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Complications – Pancreatic Leak

- Breakdown of the anastomosis of the graft to the bladder or intestine
- Fistula formation
- Accounts for technical failure of up to 10% of cases
- Conversion from bladder to enteric drainage
- Efficacy for octreotide as prophylaxis agent conflicting
- Bladder Drained Pancreas
 - n=17 (14 SPK, 1 PTA, 2 PAK)
- Enteric Drained Pancreas
 - n=40 (35 SPK, 5 solitary pancreas)

Octreotide 100µg TID x 5 days	Placebo	p-Value
0 Events	1 leak 2 IAI/pancreatitis	0.05

Octreotide 100µg TID x 7 days	Placebo	p-Value
Fistula development - 2 (10%)	0	0.46
Pancreatitis - 1 (5%)	0	0.24

Clin Transplant 2005;19:299-303

Am J Surg 1998;175:14-7

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Complications – Diabetes Development

- Autoimmune Recurrence
 - Up to 10% incidence
 - Diagnosis
 - Loss of insulin secretory function
 - Need for exogenous insulin
 - Presence of autoantibodies
 - **GAD, ICA, IA2, anti-insulin**
 - Confirmatory biopsy
 - No standard treatment
 - Anti-B or anti-T cell therapies
 - Steroids, plasmapheresis
 - Graft loss reported as 2.5%-11.8%
- Post-transplant Diabetes Mellitus (PTDM)
 - Contributors
 - Insulin resistance, reduction in insulin secretory reserve capacity, inadequate B-cell mass
 - Exacerbated by tacrolimus, steroids
 - Obesity – 10% weight gain at 1 year [IQR 2.7%-19.3%]
 - PTDM n=28 (19%), 82% T1DM at baseline
 - Time to development 87d (IQR 2.5-310d)
 - Risk factors
 - Pre-transplant insulin dose ($p<0.0001$), BMI ($p=0.0002$), acute rejection ($p<0.02$)

Ann Transplant 2019;24:608-16; *Curr Diab Rep* 2011;11:413-9
Am J Transplant 2008;8:175-82; *Transplantation* 2020;104:632-9

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Impact on Diabetes Complications

Retinopathy	Neuropathy
<ul style="list-style-type: none"> Generally favorable effects in slowing progression 	<ul style="list-style-type: none"> Improved nerve conduction velocities and mean motor and sensory indexes compared to pre-transplant
Nephropathy	Macrovascular Complications
<ul style="list-style-type: none"> Biopsies from T1DM SPK to Living Donor KT_x, 10 years post-transplant <ul style="list-style-type: none"> SPK protective from early structural changes from DM nephropathy SPK higher GFR at follow-up PTA associated with reduced proteinuria from baseline 	<ul style="list-style-type: none"> SPK vs Living Donor KT_x <ul style="list-style-type: none"> No reduction in all-cause mortality 35% reduction in CV death, $p<0.05$ SPK vs KT_x <ul style="list-style-type: none"> MI: 16% vs 50% CVA: 16% vs 40% Amputations: 16% vs 30%

Curr Opin Nephrol Hyperten 2016;25:563-69; *Transpl Int* 2005;18:1054-60; *BMJ* 2017;357:j1321

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Islet Cell Transplantation

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History and Background

- Timeline
 - **1893** – Pieces of sheep pancreas to 13 year old dying from ketoacidosis
 - **1972** – Glycemic control with infusion of islets into diabetic rat
 - **1980** – Auto-islet cell transplant in 10 patients with surgically-induced diabetes
 - Insulin independence achieved in 3 patients at 1, 9, and 38 months
 - **1988** – Ricordi® Chamber
 - **1990** – First case of insulin independence after allotransplantation in with immunosuppression
- **2000** – Edmonton Protocol
 - N=7, T1DM
 - Daclizumab, tacrolimus, sirolimus
 - Insulin independence for > 1year
 - Sustained C-peptide production
- Long-term outcomes
 - Insulin independence lost by 3-5 years
 - 10% insulin independent at 5 years
 - 80% with C-peptide secretion and A1c <7%

Islets 2018;10:80-94
NEJM 2000;343:230-8

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Current State of Islet Cell Transplant

- In US, allogenic islets considered biologic drugs regulated by FDA
 - 11 patients underwent islet cell transplant between 2016-2019
- May 2020
 - CellTrans resubmitted Biologics License Application to FDA
- April 15, 2021
 - Cellular, Tissue, and Gene Therapies Advisory Committee of FDA endorsed **donislecel (Lantidra)**, a biologic product of purified allogenic islets of Langerhans
- FDA approval pending
- 2019 AST/ASTS called upon FDA to update regulations similar to autologous islets
- Future of islet cell transplant remains unknown

Am J Transplant 2021;21:2625-6

Am J Transplant 2021;21:1365-75

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Islet Cell Transplant Outcomes

- Collaborative Islet Transplant (CIT) Registry – 10th Annual Report
 - Infusions through 9/2015
- | CITR Report | Recipients | Infusions | Donors |
|-------------------------|------------|-----------|--------|
| 1 st (2004) | 86 | 158 | 173 |
| 10 th (2015) | 1086 | 2150 | 2619 |
- Types
 - 877 islet transplant alone (ITA)
 - 183 islet after kidney (IAK)
 - 24 simultaneous islet kidney (SIK)
 - 2 kidney after islet (KAI)
 - Outcomes
 - Insulin independence
 - 50% at 1 year for ITA and IAK
 - Recipient age > 35 (p=0.006), IL2RA (p<0.0001)
 - A1c < 7%
 - ~75% ITA vs ~65% IAK at 1 year
 - ~60% ITA vs ~50% IAK at 5 years
 - C-peptide ≥ 0.5ng/mL
 - Severe hypoglycemia
 - Complete islet graft failure

www.citregistry.org. Accessed March 27, 2022

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Long-Term Clinical Outcomes

Outcome	Results
Survival	49 T1DM - Islet Cell Transplant, followed from 2000 – 2020 <ul style="list-style-type: none"> Duration of graft function (median) - 4.4 years Survival <ul style="list-style-type: none"> 2 deaths (MI, hypoglycemia) Cumulative proportion survival: 100% at 10 years, 80% at 20 years Incidence rate of mortality: 3.28 per 1000 person years
Graft Function	28 T1DM - ITA or IAK <p>Primary Outcome: Insulin Independence with A1c \leq 6.5%</p> <ul style="list-style-type: none"> 39% at 5 years and 28% at 10 years <p>Persistence of graft function</p> <ul style="list-style-type: none"> 82% at 5 years and 78% at 10 years

Diabetes Care 2021;44:e67-e68

Diabetes Care 2019; 42:2042-9

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Indications and Allocation of Islet Cell Transplant

- Islet Cell Transplantation
 - T1DM complicated by hypoglycemic unawareness, severe hypoglycemic episodes AND/OR glycemic liability
 - Considerations
 - Duration of T1DM > 5 years and \geq 18 years of age
 - Avoid in BMI > 30 kg/m², weight > 90 kg, daily insulin requirement of >1.0 unit/kg
- Auto-Islet Cell Transplantation
 - Chronic pancreatitis with total pancreatectomy
- UNOS Listing Criteria
 - Insulin Dependence
 - A1c > 6.5%
- Allocation
 - Time on waitlist
 - Distance between transplant center and donor hospital

Nat Rev Endocrinol 2017;13:268-77

OPTN Policy 11: Allocation of Pancreas, Kidney-Pancreas, and Islets. Accessed 3/30/2022

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Islet Cell Procedure

- Pancreas procurement
 - Deceased donor human islets
 - Pancreatic capsular integrity w/maximal blood supply
- Donor selection
 - Similar to solid pancreas transplant with increased allowable BMI
 - Age 20-50 years
 - BMI >30 kg/m² with A1c < 6.5%
 - Normal BG at time of donation
- Islet isolation
 - Enzyme digestion, purification via centrifuge, islet cell incubation
- Volume
 - > 5000 islet equivalents (IE)/kg
 - > 7000 IE/kg from single donor preferred
- Transplantation
 - Islet cell culture suspended in transplant media in sterile bag
 - Infusion by gravity via percutaneous cauterization of the portal vein
 - Engraftment in the liver

Nat Rev Endocrinol 2017;13:268-77

JAMA 2005;293:830-5

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Islet Cell Transplantation Complications

- Bleeding
 - Thrombostatic paste
- PV thrombosis
 - Heparin infusion x 48 hours
 - aPTT goal 60-80 sec
 - Enoxaparin 30 mg BID x 7 days
 - Aspirin EC 81 mg x 14 days
- Pain most common complication
 - Site of intrahepatic catheter
 - Referred pain in 50% of patients
- Mild AST/ALT elevations
 - Occur in 50% of patients
 - Resolution by 1 month
- Sensitization to HLA antigens
 - Increased risk with more donors
 - Use of depleting induction and tacrolimus maintenance

Nat Rev Endocrinol 2017;13:268-77

Transplantation 2010;89:465-71

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Peri-transplant Management

Anti-TNF

- Etanercept 50mg IV x 1 pre, then 25mg subq twice weekly for 2 weeks
- Etanercept 50mg IV x 1 pre, then 25mg subq on days 3, 7, and 10

IL-1 Receptor Antagonist

- Anakinra 100mg IV x 1 pre, then 100mg subq daily x 7 days

Heparin

- Heparin x 48 hours (aPTT goal 70-90 seconds)

Insulin

- Insulin ≥ 1 unit/hr, then subq insulin

Modified Edmonton Protocol 2005

- Results
 - Insulin independence (II), n=13 (15.3%)
 - Insulin and heparin associated with II aOR 8.6 (95% CI 2.0-37.0)

*JAMA 2005;293:830-5; Transplantation 2008;86:1658-65
 Clin Transplant 2012;26:e471-84; Transplantation 2010;89:465-71*

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Islet Cell Transplant Management

- GLP-1 Receptor Agonist
 - Used to augment insulin production by islets
- Graft dysfunction
 - N=11, exenatide start 17 ± 6 mo
 - 6/11 on insulin (6-20 mo at start)
 - 10 responded to exenatide
 - 2 remained off insulin, 1 never initiated insulin, 7 reduced insulin dose by 39%
 - N/V most common side effects
 - No evidence of a trophic effect on islets

- GLP-1 Receptor Agonist Use Early
 - N=6, Edmonton vs. UIC protocol
 - Addition of etanercept and exenatide
 - Outcome – insulin independence (II)
 - Exenatide
 - 5 μ g BID x 1 week, then 10 μ g BID x 6 mo

	Edmonton	UIC
II at 15 mo	4/4	4/6
Mean islets	1,460,080 \pm 418,330	537,495 \pm 190,968
Baseline A1c	7.2 \pm 1.1%	7.8 \pm 1.0%
A1c	5.9 \pm 0.4%	6.1 \pm 0.3%

*Transplantation 2007;83: 24–28
 Am J Transplant 2008;8:1250-61*

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Comparative Outcomes

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Pancreas vs. Islet Cell Transplant for T1DM

- PT (n=141) vs. ITA (n=272)
 - Mean duration of DM 30.6 ± 10.8 yrs
 - Mean A1c $8.4 \pm 1.2\%$

	PT	ITA
Female	34%	55.9%
Age at transplant, yr	41	48.4

	PT	ITA	p-value
Δ A1c at 3 months, % \pm SD	5.6 ± 0.7	6.6 ± 0.8	0.01
Δ A1c up to 15 years, % \pm SD	6.1 ± 0.8	7.3 ± 1.4	0.01
Insulin Independence, %	95	77.2	<0.001
Follow-up time off insulin, % \pm SD	92.3 ± 18.5	46.6 ± 31.2	<0.001
Hospital admissions, n \pm SD	1.7 ± 1.2	1.2 ± 0.7	0.009
1 year mortality, %	3.6	0	0.002

Diabetes 2020;69(Supplement_1):116-OR

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Question 1: Which of the following is true about graft pancreatitis?

- A. Most commonly occurs after 3 months
- B. Late graft pancreatitis is a common cause of graft loss
- C. Antibiotics have no role in the treatment of graft pancreatitis
- D. Donor age > 50 and DCD grafts have been associated with early graft pancreatitis

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Question 2: When is it appropriate to monitor urinary amylase/lipase?

- A. In a patient with a bladder drained pancreas
- B. In a patient complaining of cystitis
- C. In a patient with a bladder drained pancreas converted to enteric drained
- D. In all patients

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Question 3: What of the following is true about pancreas vs. islet cell transplantation?

- A. Pancreas transplantation is associated with increased insulin independence
- B. Islet cell transplantation does not require maintenance immunosuppression
- C. The pancreas transplant procedure is considered a less invasive procedure compared to the islet cell procedure
- D. Islet cell transplantation is associated with less HLA sensitization compared to pancreas transplantation

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Key Takeaways

- Pancreas transplantation is a viable treatment option for insulin-dependent diabetes with or without end stage renal disease
- Pancreas transplant carries a high immunological risk
- Improvements in surgical technique, treatment of acute complications, and immunosuppression have improved graft survival rates
- Islet cell transplantation is a less invasive alternative to pancreas transplantation but is associated with decreased incidence of insulin independence

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Pancreas and Islet Cell Transplantation

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Intestinal Transplantation

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- I have nothing to disclose relevant to this presentation.

43

Learning Objectives

- Describe the etiologies of intestinal transplantation
- List the current trends in immunosuppression for intestinal transplantation
- Discuss the common complications observed after intestinal transplantation

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Indications and Types of Small Bowel Transplantation

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Types of Intestinal Transplantation

Isolated small-intestine graft (ITx)

Involves transplantation of the jejunum with systemic drainage to the vena cava.

Composite liver–small-intestine graft (LITx)

Includes the duodenum and an intact biliary system and portal circulation with the native foregut preserved.

Multivisceral graft (MVTx)

Involves the liver, stomach, duodenum, pancreas, and small intestine.

May also include colon and/or kidney.

N Engl J Med. 2009;361(10):998–1008.

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Intestinal Transplantation: Graft and Patient Survival

- Patient survival at 1 year for transplants in 2013-2015 was higher for recipients of an intestine alone versus intestine-liver transplant (83.7% vs 75.6%)
- By 5 years, the patient survival was identical, at 58.7% for both allograft types (adult recipients)

Am J Transplant. 2022 Mar;22 Suppl 2:310-349. doi: 10.1111/ajt.16992.

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Permanent intestinal failure(IF)

- Anatomic or functional reduction of the intestinal mass so that nutritional requirements for fluids, macro-, and micronutrients are not met leading to severe dehydration and malnutrition
- Parenteral nutrition is the gold standard treatment for benign chronic IF
- About 50% of adult patients with benign chronic IF can achieve enteral autonomy within the first 2 years.
 - After that significant adaptation occurs, up to 94% of the adult patients have the probability of permanent IF requiring life-long PN
- Pediatric patients, intestinal adaptation and enteral autonomy can occur over a prolonged period in sharp contrast to adult.

Gastroenterol Clin N Am 2019; 48: 575–583.
 Gastroenterology 1999;117(5):1043–50.
 Ann Surg 2005;242(3):403–9.

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Indications for Intestinal Transplant

- 2001 Centers for Medicare and Medicaid Services (CMS) memorandum defined PN failure the following way:
 - Impending (total bilirubin 3–6 mg/dL, progressive thrombocytopenia, and progressive splenomegaly) or apparent liver failure (portal hypertension, hepatosplenomegaly, hepatic fibrosis, or cirrhosis) because of PN liver injury.
 - Central venous catheter–related thrombosis of 2 central veins.
 - Frequent central line sepsis: 2 episodes per year of systemic sepsis secondary to line infections requiring hospitalization; a single episode of line-related fungemia; septic shock; or acute respiratory distress syndrome.
 - Frequent episodes of severe dehydration despite intravenous fluid in addition to PN

<https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/downloads/AB02040.pdf>

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Additional Indications for Intestinal Transplant

- American Society of Transplantation proposed indications for intestinal transplantation in addition to PN failure
 - Desmoid tumors associated with familial adenomatous polyposis
 - Congenital mucosal disorders (microvillus atrophy and intestinal epithelial dysplasia)
 - Ultrashort bowel syndrome (gastrostomy, duodenostomy, residual small bowel 10 cm in infants and 20 cm in adults)
 - IF with high morbidity (frequent hospitalization, narcotic dependency) or inability to function (pseudo-obstruction, high-output stoma)
 - Patient's unwillingness to accept long-term PN (young patients)

Gastroenterology 2003;124(4):1111–34.
 Pediatr Transplant 2001;5(2):80–7.

50

Intestinal Transplant Organ Allocation

- **Intestinal organ allocation**
 - Status 1 criteria
 - Liver function test abnormalities
 - No longer has vascular access through the subclavian, jugular, or femoral veins for intravenous feeding
 - Medical indications that warrant intestinal organ transplantation on an urgent basis.
 - Status 2 criteria
 - All candidates who do not meet the criteria for Status 1 are Status 2
- **Combined intestine-liver allocation**
 - According to the liver allocation system (MELD/PELD)

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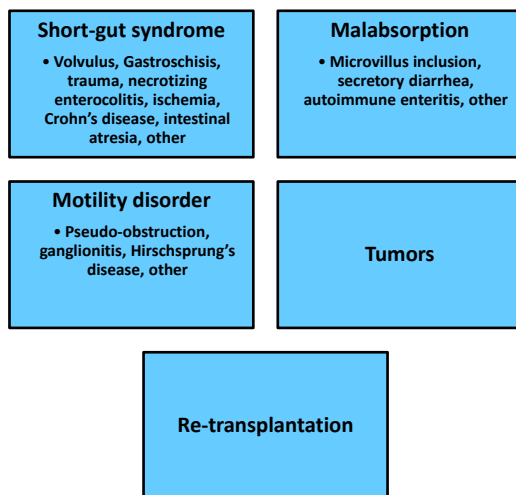
Factors Influencing Long-Term PN

Decreasing Survival	Decreasing Rehabilitation
Age > 60 years at initiation of therapy	Jejunioileal length < 50 cm
Jejunioileal length < 50 cm	Absence of ileocecal valve
Dysmotility	Mucosal disease
Radiation enteritis	Dysmotility
More severe obstruction	Abdominal-wall defect in children
Longer treatment	

N Engl J Med. 2009;361(10):998–1008.

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Distribution of Diseases



- Most common etiology of intestinal failure remains short-gut syndrome (SGS) (51.1%)
- Intestine transplant candidates: Pseudo-obstruction, necrotizing enterocolitis, and non-congenital SGS
- Intestine-liver candidates: enteropathies and congenital SGS
- Intestine-liver candidates were more often status 1 than intestine candidates (52.9% vs. 32.7%).

N Engl J Med. 2009;361(10):998–1008.
 Am J Transplant. 2022 Mar;22 Suppl 2:310–349. doi: 10.1111/ajt.16992.

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Pharmacological Gut Rehabilitation

Drug	Teduglutide (Gattex)
Class	Glucagon-like peptide 2 (GLP-2) receptor analog (growth hormone)
Mechanism of Action	<ul style="list-style-type: none"> • Naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cells of the distal intestine. • Increase intestinal and portal blood flow and inhibit gastric acid secretion. • Teduglutide binds to the glucagon-like peptide-2 receptors located in intestinal subpopulations of enteroendocrine cells, subepithelial myofibroblasts and enteric neurons of the submucosal and myenteric plexus. • Activation of these receptors results in the local release of multiple mediators including insulin-like growth factor (IGF)-1, nitric oxide, and keratinocyte growth factor (KGF).
Dose	0.05 mg/kg (actual body weight) SC daily • CrCl < 60 mL/min: 0.025 mg/kg SC daily
Warnings and ADEs	<ul style="list-style-type: none"> • Acceleration of neoplastic growth • Intestinal obstruction • Increased absorption of oral medications (potential)

Teduglutide [package insert]. Lexington, MA: Takeda Pharmaceutical Company. Revised January 2021.

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Immunologic Considerations of the Intestinal Allograft

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Immunologic Risks

- Approximately **80% of immune cells normally reside in the gut** and are repopulated after transplant with **recipient cells**
- Epithelium genotype remains **largely that of the donor**, making the organ **highly chimeric and immunogenic**
- Gut relies on barrier and other immunologic mechanisms to provide protection against invasion by extensive commensal flora
- **Breach of this barrier** by ischemia or reperfusion injury, by recipient immune cells, or by defects results in **inflammation and tissue damage** and increases the likelihood of **infection**
- Loss of immunologic protection makes the augmented immunosuppression required to treat rejection **particularly dangerous**

N Engl J Med. 2009;361(10):998–1008.
 J Pediatr Gastroenterol Nutr 2000;30:Suppl:S4-S12.
 Am J Transplant 2003;3:1-2.

56

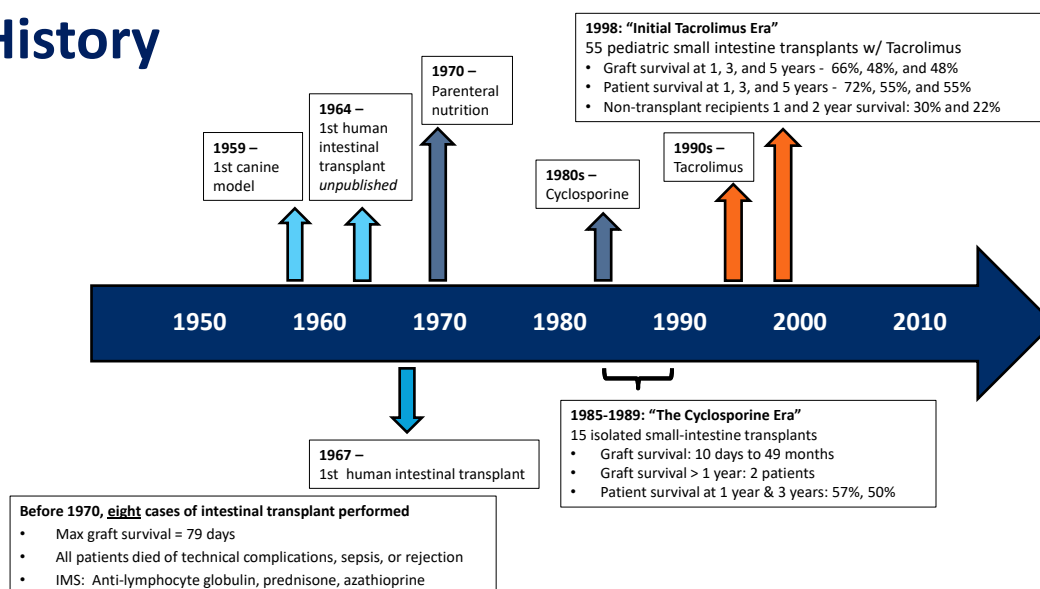
Immunologic Response to the Donor Allograft

- Naive T cells infiltrate the allograft and undergo priming and activation in the donor mesenteric lymph nodes and Peyer's patches
 - Other organs, priming occurs primarily in recipient lymphoid tissues
- Donor antigen-presenting cells then ingest and display the “foreign” graft antigens in association with major histocompatibility complex (MHC) class I and II molecules
 - Antigen-presenting cells are stimulated to express costimulatory effectors to “arm” naive CD8+ cytotoxic T cells and predominantly CD4+ type 1 helper T cells (Th1 cells)
 - The CD8+ cytotoxic T cells attack certain donor-cell targets and produce substances (perforin, granzyme, and Fas ligand) that lead to crypt-cell apoptosis
 - Armed Th1 cells provoke an inflammatory state driven by the production of cytokines
 - The dendritic cell also maintains immune defenses of the epithelium by regulating secretion of the antimicrobial peptide human defensin 5 from Paneth cells by means of NOD2-dependent circuits.

N Engl J Med. 2009;361(10):998–1008.

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History



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Anti-Rejection Medication Regimens in the Intestinal Transplant Recipient

59

Induction and Maintenance Immunosuppression

- Induction
 - T-cell depleting (TCD) induction (59%), interleukin-2 receptor antagonist (IL2RA) induction (14%), no induction therapy (30%)
- Maintenance
 - Tacrolimus (used in at least 73% of recipients)
 - Combined with corticosteroids (37.4%), mycophenolate mofetil (6.6%), or both (29.7%)

N Engl J Med. 2009;361(10):998–1008.
 Am J Transplant. 2022 Mar;22 Suppl 2:310-349. doi: 10.1111/ajt.16992.

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Acute Rejection at 1 Year

- The incidence of first acute rejection in the 1st year post-transplant varied by age group and transplant procedure
- Among recipients in 2018-2019, incidence of acute rejection was **highest** in **adult intestine recipients** (41.2%) and **lowest** in **adult intestine-liver recipients** (35.4%)

N Engl J Med. 2009;361(10):998–1008.
Am J Transplant. 2022 Mar;22 Suppl 2:310-349. doi: 10.1111/ajt.16992.

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Immunosuppression Specific Data

Limited to single-center experiences

Many retrospective studies

SRTR databases to guide immunosuppression trends

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Alemtuzumab Induction

Study	Year	Design	n	Results
Garcia M, et al.	2004	R C	Alemtuzumab (n = 27); Dacalizumab (n = 51)	<ul style="list-style-type: none"> • Reduced incidence of ACR in alemtuzumab vs dacalizumab (19.1% vs 32.8%) • Lower grade of ACR in alemtuzumab patients (p-value < 0. 01) • Patient and graft survival was similar
Nishida S, et al.	2006	R (Adult)	Non-alemtuzumab (n = 39); Alemtuzumab (n = 37)	<ul style="list-style-type: none"> • One-year survival not statistically significant • ACR was lower in alemtuzumab (p < 0.005). • Seventeen patients (81%) are steroid free, and 15 (71%) are maintained solely on tacrolimus
Zanfi C, et al.	2010	R (Adult)	Dacalizumab (n = 12); Alemtuzumab (n = 28)	<ul style="list-style-type: none"> • ACR lower in alemtuzumab arm (dacalizumab 66% vs. alemtuzumab 42.8%) • Bacterial infections (dacalizumab 66.6% vs. alemtuzumab 57.1%) • Five-year graft survival (dacalizumab 66% vs alemtuzumab 41%, p = NS)

Transplant Proc. 2004 Mar;36(2):323-4.
 Transplant Proc. 2002 Aug;34(5):1889-91.
 Transplant Proc. Jan-Feb 2010;42(1):35-8.

R = retrospective

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Rabbit Anti-thymocyte Globulin and Interleukin-2 Receptor Antagonist Induction

Study	Year	Design	n	Results
Farmer DG, et al.	2004	R (pediatric and adult)	No induction (n = 10); IL2RA (n = 13); OKT3 (n = 4)	<ul style="list-style-type: none"> • IL2RA had significantly fewer rejection and infectious episodes vs the other two groups (p<0.05 for both) • Age-normalized sCR was lower in IL2RA vs the other two groups (p<0.01) • Three-year graft survival was 92% (IL2RA) vs 20% (no induction) vs 25% OKT3)
Reyes, et al.	2005	R (pediatric and adult)	rATG (n = 36)	<ul style="list-style-type: none"> • ACR in the first month occurred in 44% • 1- and 2-year patient/graft survival is 100% and 94% • Survivors are on TAC (n = 14) monotherapy; TAC plus low dose prednisone (n = 15) most commonly
Vianna RM, et al.	2008	R (age not specified)	rATG/Rituximab (n = 27)	<ul style="list-style-type: none"> • One-year patient and graft survival was 81% and 76%, respectively • Thirteen patients (48%) experienced 19 episodes of acute rejection

Transplant Proc. 2004 Mar;36(2):331-2.
 Am J Transplant. 2005 Jun;5(6):1430-6.
 Transplantation. 2008 May 15;85(9):1290-3.

R = retrospective

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Five Hundred Intestinal and Multivisceral Transplantations at a Single Center

Study	Year	Design	n	Results
Abu-Elmagd, et al.	2009 (pediatrics and adult)	R	Whole cohort (n = 453)	<ul style="list-style-type: none"> Actuarial patient survival was 85% at 1-year, 61% at 5-years, 42%, at 10-years, and 35% at 15-years with respective graft survival of 80%, 50%, 33%, and 29%.
			<u>Era I</u> tacrolimus-steroid-only	<ul style="list-style-type: none"> Best outcome was with <u>intestine-liver allografts</u>
			<u>Era II</u> induction with multiple drug therapy	<ul style="list-style-type: none"> Era III rabbit antithymocyte globulin or alemtuzumab pretreatment-based strategy was associated with <u>significant improvement in outcome with 1- and 5-year patient survival</u> of 92% and 70% (p < 0.0001)
			<u>Era III</u> pretreatment with tacrolimus monotherapy and BM augmentation	<ul style="list-style-type: none"> Survival of the bone marrow augmented grafts was <u>similar</u> (p = 0.80) to the contemporaneous controls

R = retrospective

Annals of Surgery, 2009; 250(4), 567-81.

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Association of More Intensive Induction With Less Acute Rejection Following Intestinal Transplantation

Study	Year	Design	Whole cohort (n=445)	Results
Vianna RM, et al.	2020	R (pediatric and adult)	<u>Group 1 (n = 44)</u> OKT3, cyclophosphamide, or no induction	<ul style="list-style-type: none"> Incidence of ACR (61.3%) and severe ACR (22.2%)
			<u>Group 2 (n = 159)</u> IL2RA induction	<ul style="list-style-type: none"> Multivariable predictors associated with less ACR development and severe ACR: <ul style="list-style-type: none"> <u>MVTx</u> (p=0.0009 and p<0.000001), <u>rATG/rituximab</u> (p<0.000001 and p < 0.01), and <u>alemtuzumab</u> (p=0.004 and p=0.07)
			<u>Group 3 (n = 113)</u> Alemtuzumab induction	<ul style="list-style-type: none"> rATG/rituximab and alemtuzumab were <u>protective during the first 6 months</u> post-transplant for <u>graft loss-due-to-rejection</u> (p=0.01 and p=0.003)
			<u>Group 4 (n = 34)</u> rATG induction	
			<u>Group 5 (n = 95)</u> rATG/ rituximab induction (+ basiliximab in select few)	<ul style="list-style-type: none"> rATG/rituximab was associated with <u>lower rates</u> of graft loss-due-to-infection (p=0.003)

R = retrospective

Transplantation. 2020 Oct;104(10):2166-2178.

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Intestinal Transplantation and Sirolimus

Study	Year	Design	n	Results
Fishbein TM, et al.	2002	R (pediatric and adult)	Pediatric (n = 18)	<ul style="list-style-type: none"> The incidence of biopsy-proven rejection in the first 30 days was lower in those patients placed on sirolimus (73.7% vs 16.7%, p<0.002)
			Adult (n = 11)	
			<u>Group 1 (n = 19)</u> Tacrolimus, steroids, and daclizumab or OKT3	<ul style="list-style-type: none"> Actuarial 1-year graft survival was higher with sirolimus (91.7% vs 57.9%, p<0.04) Actuarial 1-year patient survival was similar between the groups (p=0.12) Sirolimus was temporarily held or discontinued in many (66.7%) patients
			<u>Group 2 (n = 12)</u> Tacrolimus, steroids, basiliximab, and sirolimus	

R = retrospective

Transplantation. 2002 May 27;73(10):1538-42.

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Intestinal Transplantation and Corticosteroids

Study	Year	Design	Whole cohort (n = 25)	Results
Dazzi A, et al.	2007	R (Age not specified)	Groups compared by prednisone dose (cut-off limit of 20 mg/day of prednisone)	<ul style="list-style-type: none"> Number of rejections was similar between those patients on < 20 mg/day of prednisone or > 20mg/day of prednisone Patients with a mean dosage of prednisone > 20 mg/day experienced lower graft survival (p = 0.009) and patient survival (p = 0.02) rates The side effects of steroids after transplant were similar Infections were more frequent during steroid administration (p = 0.04)
			Daclizumab (n = 13)	
			Alemtuzumab (n = 10)	
			Thymoglobulin (n = 2)	

R = retrospective

Clin Transplant. 2007 Mar-Apr;21(2):265-8.

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Intestinal and Multivisceral Transplantation Immunosuppression Protocols– Literature Review

Study	Year	Design	Whole Cohort (n = 211)	Results
Trevizol AP, et al.	2012	Systematic review and analysis (Age not specified)	<u>Protocol 1</u> Daclizumab with tacrolimus/ steroids <u>Protocol 2</u> Alemtuzumab and tacrolimus <u>Protocol 3</u> rATG/ rituximab and tacrolimus	<ul style="list-style-type: none"> Protocol 2 showed the lowest rate of ACR (34%). Protocols 1 and 3 displayed 54% and 48% ACR rates Infection rate was considerably lower in protocol 3 (7.4%). Protocols 1 and 2 showed infection rates of 62.5% and 52%, respectively One-year patient survival rates were 70%, 79% and 81%, respectively Three-year patient survival rates were 62%, 56%, and 78% for protocols 1, 2 and 3, respectively

R = retrospective

Transplantation Proceedings, 2012; 44(8), 2445-8.

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Intestinal Transplant Registry Report: Global Activity and Trends

Study	Year	Design	n	Results
Grant D, et al.	2015	Registry	Whole cohort (n = 2,699) 82 contributing centers, 95% of all cases ever performed	<ul style="list-style-type: none"> Current actuarial patient survival rates are 76%, 56% and 43% at 1, 5 and 10 years, respectively Factors predicted for better graft survival in a multivariate Cox Proportional Hazards Model: <ul style="list-style-type: none"> Waiting at home for IT, induction therapy, inclusion of a liver component, and maintenance therapy with rapamycin were associated with better graft survival Identifying the root reasons for late graft loss is difficult due to the low case volumes at most centers

American Journal of Transplantation. 2015 15, 210-9.

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Rejection Diagnosis and Management

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Histological Criteria: Acute Cellular Rejection

Grade	Details
Grade Ind (Indeterminate)	Minimal localized inflammatory infiltrate, minimal crypt epithelial injury, increased crypt epithelial apoptosis (usually with 6 apoptotic bodies/10 crypts), no to minimal architectural distortion, no mucosal ulceration, changes insufficient for the diagnosis of mild acute rejection (Score = 1)
Grade 1 (Mild)	Mild localized inflammatory infiltrate with activated lymphocytes, mild crypt epithelial injury, increased crypt epithelial apoptosis (usually with 6 apoptotic bodies/10 crypts), mild architectural distortion, no mucosal ulceration (Score = 2)
Grade 2 (Moderate)	Widely dispersed inflammatory infiltrate in lamina propria, diffuse crypt epithelial injury, increased crypt apoptosis with focal confluent apoptosis, more prominent architectural distortion; possible mild to moderate intimal arteritis; no mucosal ulceration (Score = 3)
Grade 3 (Severe)	Features of moderate ACR plus mucosal ulceration; possible severe intimal arteritis or transmural arteritis may be seen. Diffuse mucosal erosion/ulceration are present. Loss of the bowel morphological architecture with mucosal sloughing and "exfoliative" rejection. Arteritis may be evident, but this is an uncommon finding (Score = 4)

Transplant Proc. 2004 Mar;36(2):335-7.
 Transplantation. 2003 Apr 27;75(8):1241-8.

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Agents for Intestinal Allograft Rejection

- Corticosteroids
 - First-line for mild rejection
 - Typically “pulse” therapy is utilized
- Anti-thymocyte globulin and alemtuzumab
 - Reserved for severe or steroid-resistant rejections
- Bortezomib
 - Salvage therapy for antibody mediated rejection, case reports
- Eculizumab
 - Salvage therapy for antibody mediated rejection, case reports
- Anti-tumor necrosis factor alpha (TNF-alpha)
 - Salvage therapy for steroid-resistant rejection, case reports
- Vedolizumab
 - Salvage therapy for steroid-resistant rejection, case reports

Gastroenterology. 2006 Feb;130(2 Suppl 1):S163-9.
 Transplant Proc. 2013 Jun;45(5):2032-3.

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Infliximab in Intestinal Transplantation

- Seen in induction and rejection treatment settings
 - Mitigate graft-associated inflammation responses and deplete recipient effector memory CD8+ T cells
- Infliximab Dosing
 - [Radke, et al \(2003\)](#): 3 mg/kg x 4 doses
 - [Pascher, et al \(2005\)](#): 3 mg/kg x4 doses
 - [De Greef, et al \(2012\)](#):
 - Pt #1: 5 mg/kg x1 dose
 - Pt #2: 4 mg/kg x1 dose, then 3 mg/kg x2 doses following
- Re-dosing was based on relapse of rejection assessed through symptomology
- Biosimilar use not well reported but clinically observed in practice

Curr Opin Organ Transplant. 2016 Apr;21(2):171-7.
 Transplant Proc. 2005 Apr;37(3):1635-6.
 J Pediatr Gastroenterol Nutr. 2012 Apr;54(4):565-7.
 Transplantation. 2003 Aug 15;76(3):615-8.

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Infliximab in Intestinal Transplant Rejection

Indication	Number of Patients	Clinical Remission
Early-onset, OKT3 resistant rejection	6	1/6 (16.7%)
Late-onset, OKT3/rATG resistant rejection	8	6/8 (75%)
Late-onset steroid-resistant rejection	3	3/3 (100%)
Chronic inflammatory mucosal lesions, ileal ulcers	22	20/22 (30.9%), 1 partial response

Infliximab has been used by several groups for four main indications. Particularly chronic inflammatory mucosal lesions and ileal ulcerations as well late-onset resistant rejections could be addressed with significant success.

Curr Opin Organ Transplant. 2016 Apr;21(2):171-7.

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Vedolizumab in Intestinal Transplant Rejection

- Humanized monoclonal antibody that binds specifically to the $\alpha 4\beta 7$ integrin
 - Inhibits T lymphocytes from binding to adhesion molecules (MAdCAM-1) expressed in the small bowel and colon
- Vedolizumab dosing
 - Norsa, et al (2017, CIRTa abstract; n = 4):
 - Induction dosing: 300 mg vedolizumab on weeks 0, 2, and 6
 - Maintenance dosing: 300 mg every 8 weeks
 - Beduschi, et al (2017, CIRTa abstract; n = 1):
 - 300 mg X 3 doses
 - Trentadue, et al (2020):
 - Induction dosing: 300 mg vedolizumab on weeks 0, 2, and 6
 - Maintenance dosing: 300 mg every 8 weeks
 - Eight infusions were given during the study period with biopsy controls

Transplantation. 2017 June; 101 (6S2): S59. doi: 10.1097/01.tp.0000521364.18534.8f

Transplant Direct. 2020 Jan 17;6(2):e527.

CIRTa = Congress of the Intestinal Rehabilitation and Transplantation Association

Transplantation. 2017 June; 101(6S2): S116

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Mortality After Steroid-Resistant Acute Cellular Rejection and Chronic Rejection Episodes

Study	Year	Design	n	Results
Lauro A, et al.	2013	R (Adults)	<u>Wole cohort</u> (n = 48 patients, n = 49 allografts)	<ul style="list-style-type: none"> Steroid-resistant ACR mortality was 50% while chronic rejection (CR) mortality was 60% Ten patients (52.6%) died after steroid-resistant ACR or CR, mostly from <u>sepsis</u> The difference in survival between steroid-resistant and CR population vs steroid-sensitive ACR and no ACR patients <u>did not achieve statistical significance</u> (p=0.47).
			<u>IL2RA induction</u> (n = 12)	
			<u>Alemtuzumab induction</u> (n = 35)	

R = retrospective

Transplant Proc. 2013 Jun;45(5):2032-3.

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Donor-Specific Antibodies After Intestinal Transplant

Study	Year	Design	N	Results
Cheng EY, et al.	2017	R (age range not specified)	Recipients (n = 95)	<ul style="list-style-type: none"> Pretransplant DSA was detected in 11% recipients with 50% continuing to have circulating antibodies post-transplant <i>De novo</i> DSA occurred in 25% of recipients and, and 71% had persistent DSA
			Transplants (n = 109)	

R = retrospective

Transplantation. 2017 Apr;101(4):873-882.

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Graft Failure and Re-Transplantation

- Rejection is a major cause of graft failure
- Abu-Elmaged, et al (47 cases)
 - 5-year survival of 47% for all re-transplant modalities
 - Re-transplantation with liver-contained visceral allograft had better 5-year survival rates (61% vs 16% for liver-free visceral grafts)
- Desai CS, et al. (analysis of Organ Procurement and Transplantation Network database)
 - Itx: patient survival was 28.5% at 5 years, which was worse than primary isolated ITx (p=0.005)
 - L-Itx : patient survival was 46.8% at 5 years and was like primary L-ITx
 - Patient and graft survival in adult L-ITx re-transplants were better in Era 2 (January 2001-August 2009) than Era 1 (October 1987-December 2000) (p=0.01)
 - Prior hospitalization was associated with higher mortality (hazard ratio 5.4, 95% confidence interval [CI], 1.92–15.62)

Transplant Proc. 2013 Apr;45(3):1133-6.
 Transplantation. 2012 Jan 15;93(1):120-5.

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Other Complications

Infections

Hypogammaglobulinemia

Diarrhea

Food allergies

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Infectious Complications after Intestinal Transplant

Infections	Information
Infectious enteritis (IE)	<ul style="list-style-type: none"> Incidence of IE 39% and was diagnosed at a median of 76 days post-ITx
Bloodstream infections	<ul style="list-style-type: none"> Bloodstream infections occurred in 34/56 patients (60.7%) 65.9% gram-positive organisms, 34.1% gram-negative organisms, and 2.4% fungi Risk factors: liver graft and a pre-operative bilirubin > 5 mg/dL Incidence of bloodstream infections was more common in children (p=0.006)
Cytomegalovirus (CMV)	<ul style="list-style-type: none"> 7% of patients experienced CMV disease and 11% experienced CMV viremia CMV disease was associated with an 11.1 times higher risk of death and shorter time-to-death after transplantation (303 days versus 1232 days) CMV enteritis further shortened the time-to-death (248 days versus 1212 days)

Pediatr Transplant. 2012 May;16(3):294-301.
 Transplantation. 2005 Mar 27;79(6):702-9.
 Transpl Infect Dis. 2012 Jun;14(3):242-7.

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Hypogammaglobulinemia

Study	Year	Design	n	Results
Farmer DG, et al.	2013	R (pediatric and adult)	34	<ul style="list-style-type: none"> Relative to pre-ITx levels, a statistically significant decrease in immunoglobulin G (IgG) levels was observed after ITx (p<0.05) Twenty patients (59%) developed hypogammaglobulinemia (HGG) during the post-ITx period at a mean of 9.8 days Numerically higher incidence of HGG in the following: isolated Itx (78%) vs MVTx (52%) (p=0.14); males (71%) vs females (38%) (p=0.05); adults (88%) vs pediatric (50%) (p=0.20); rATG induction (75%) vs IL2RA (50%) (p=0.27) Intravenous immune globulin G (IVIG) was administered to 85% of patients with HGG No significant associations were identified between HGG and either infections or ACR were observed

R = retrospective

Transplantation. 2013 May 15;95(9):1154-9.

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Other Immune Complications

- Graft-versus-host disease (GVHD)
 - High mortality (43-70%)
 - Increasing or modifying immunosuppression (limited therapy options currently)
- Inflammatory bowel disease (IBD) and *De novo* autoimmune disorders
 - 10 times that of the general population
 - Not clear whether IBD is an autonomous disorder or a different phenotype of ACR
 - Anti-TNF α and vedolizumab may have a roles in this complication
- Food allergies
 - Tacrolimus is associated with eosinophilic gastroenterocolitis secondary to food allergy, asymptomatic eosinophilia, and elevated total and specific IgE levels

Curr Opin Organ Transplant. 2012 Jun;17(3):268-72.

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Allograft Dysfunction After Intestinal Transplant

- Diarrhea
 - Standard evaluations (testing for fecal reducing substances and obtaining stool cultures to detect overgrowth) are rarely helpful
- Nutritional and dietary considerations
 - Concern for dumping syndrome
 - Foods containing insoluble cellulose or high in simple carbohydrates may cause early dumping syndrome
 - Vitamin, mineral, and micronutrient absorption is generally appropriate
 - Routine assessments are not necessary
 - Several studies in children have shown linear growth and development after a transition to enteral feeding but failed to show “catch up” from the depressed growth curves

N Engl J Med 2009;361:998-1008.

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Post-transplant Lymphoproliferative Disorders (PTLD)

- Risk factors for PTLD development
 - ITx recipients (up to 32% of recipients)
 - Primary EBV infection
 - OKT3 and polyclonal antilymphocyte antibody use
 - Young recipient age (i.e., infants and young children)
- Wozniak LJ, et al.
 - Nineteen (17%) ITx recipients developed 25 PTLD cases (follow-up time = 6.4 years)
 - The incidence of early PTLD was 6% and all cases were EBV+ on in situ hybridization
 - Significantly increased risk of PTLD in re-ITx compared with primary ITx recipients (p = 0.03)

Clin Transplant. 2018 Aug;32(8):e13313.

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Severe Chronic Kidney Disease

Study	Year	Design	n	Results
Huard G, et al.	2017	Registry (adult)	Whole cohort (n = 843)	<ul style="list-style-type: none"> • Cumulative incidence of severe CKD at 1, 5, and 10 years after ITx was reported as 3.2% (1 year), 25.1% (5 year), 54.1% (10 year), and 83.3% (15 year)
				<ul style="list-style-type: none"> • Risk factors associated with increased development of severe CKD after ITx: <ul style="list-style-type: none"> • Female gender (HR 1.34), older age (HR 1.38/10 year increment), catheter-related sepsis (HR 1.58), steroid maintenance immunosuppression (HR 1.50), graft failure (HR 1.76), ACR (HR 1.64), prolonged requirement for IV fluids (HR 2.12), TPN (HR 1.94), and diabetes (HR 1.54)
				<ul style="list-style-type: none"> • Risk factors associated with less development of severe CKD after ITx: <ul style="list-style-type: none"> • Higher GFR at the time of ITx (HR 0.92 per each 10 mL/min/1.73 m² increment), induction immunosuppression (HR 0.47), and tacrolimus (HR 0.52)
Reyes, et al.	2005	R (adult)	Whole cohort (n = 280)	<ul style="list-style-type: none"> • Severe CKD was associated with a significantly higher hazard of death (HR 6.20)
				<ul style="list-style-type: none"> • Increased ESRD risk factors: Higher baseline creatinine (HR 3.40), liver containing grafts (HR 2.01) • Median patient survival after dialysis initiation was 6 months, with a 3-year survival of 21%. Any dialysis (HR 12.74) and ESRD (HR 9.53) had higher mortality. • Renal transplant after ITx 1- and 3-year kidney and patient survivals were 70% and 49%, respectively

Clin Transplant. 2017 May;31(5). doi: 10.1111/ctr.12942.

Transplant Direct. 2018 Jul 20;4(8):e377. doi: 10.1097/TXD.0000000000000815

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Self Assessment Question #1

Which of the following is not a component of the 2001 Centers for Medicare and Medicaid Services (CMS) memorandum definition of PN failure?

- A. Impending or apparent liver failure
- B. Catheter-related thrombosis of 2 central veins
- C. Single episode of line-related fungemia
- D. Patient's unwillingness to accept long-term PN

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Self Assessment Question #2

GG is a 42 yo liver-intestinal transplant recipient from 4 months ago. She reported for biopsy of her allograft after feeling ill and reporting diarrhea and bloody bowel movements x 3 days. She is DSA negative and preliminary biopsy finding demonstrate severe ACR. Which of the following would be the most appropriate agent to initiate for her rejection episode?

- A. Belatacept
- B. Eculizumab
- C. Anti-thymocyte globulin
- D. Infliximab

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Self Assessment Question #3

Which of the following is not a risk factor for the development of PTLT after intestinal transplantation?

- A. LITx recipients
- B. Primary EBV infection
- C. OKT3 and polyclonal antilymphocyte antibody use
- D. Young recipient age

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Key Takeaways

- Intestinal transplant is a complex surgery for those patients with IF and PN failure
- Immunosuppression regimens are highly variable but most commonly include anti-lymphocyte depleting induction and maintenance immunosuppression with tacrolimus and prednisone
- There are numerous complications after intestinal transplant that pharmacists should be aware of as a component of their acute and chronic care

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