	Islet Transplant	Renal Transplant	Liver Transplant	Lung Transplant
Transplant Eligibility				
Reasons for Transplant	Type 1 DM complicated by severe hypoglycemia and/or hypoglycemia unawareness (73%) • Consider number and frequency of episodes, need for 3rd party assistance, presence/absence of adrenergic or neuroglycemia • HYPOscore Severe glycemic instability (22%) • Lability index (LI) Either of the above, despite optimization of medical therapy • Carbohydrate counting • Multiple daily injections • Pump therapy • Long/short acting insulin analogues	ESRD Stage 5 (CrCl < 20 mL/min) arising from: • Glomerulonephritis (#1 overall most common cause overall, more in young patients) • Diabetes (#2 most common cause overall, more in elderly patients) • Hypertension • Polycystic kidney disease • Abnormalities with the urinary tract (urine refluxes into kidney, causes damage) • Obstruction (renal stones) • Tubular disorders • Various autoimmune disorders such as lupus, IgA nephropathy, HUS • Damage induced by nephrotoxic agents (amphotericin B) • Cancer (Renal cell carcinoma, Wilm's tumor) • Congenital disorders • Focal glomerulonecrosis	Chronic Liver Diseases • Hepatocellular Disorder ◦ **Hepatitis C: most common reason for liver transplant** ◦ Hepatitis B ◦ Cryptogenic ◦ **Alcohol: second-most common reason for liver transplant** ◦ Autoimmune cirrhosis • Cirrhosis: end-stage hepatic fibrosis ◦ Disordered architecture ◦ Regenerative nodules • Cholestatic Disorders ◦ Primary biliary cirrhosis ◦ Primary sclerosing cholangitis Acute • Fulminant hepatic failure ◦ Rapid development ◦ Severe impaired liver function (from normal functioning) ◦ Causes • Hepatitis A • Hepatitis B • Drug toxicity • Wilson's Disease • Tumours ◦ **Hepatocellular carcinoma: third-most common reason for liver transplant** ◦ Specific criteria for: • Size • Number of tumours • Spread to blood vessels	Obstructive Disease • α1-antitrypsin • **Emphysema** • Obliterative bronchiolitis • Broncho-pulmonary dysplasia • Pulmonary talcosis Suppurative • **Cystic fibrosis** • Bronchiectasis Restrictive • **Idiopathic pulmonary fibrosis** • Sarcoidosis • Pneumoconiosis • Other interstitial lung diseases Vascular • Primary pulmonary hypertension • Secondary pulmonary hypertension • Eisenmenger's syndrome • Pulmonary venocclusive disease

Requirements	• Type 1 diabetes
	• C-peptide negative
	• Weight < 90kg
	• Insulin dose < 1 unit/kg/day
		• ESRD Stage 5 (CrCl < 20 mL/min)
		• Adherence to medications
		• No substance abuse
			MELD Score
			• **↑ MELD = ↑ Mortality**
			• Measure of cirrhosis prognosis
			• Criteria
			  ○ Serum bilirubin
			  ○ INR
			  ○ SCr
			• Calculation not likely to be tested
			Note: the Child-Pugh scoring system is used to evaluate cirrhosis but not to determine liver transplant eligibility
				• Receiving maximal medical therapy
				• No absolute contraindications
				• Life expectancy ≤ 2 years
				• No other untreatable conditions that would preclude a satisfactory outcome
				• Ability to be compliant with medications
				• Adequate resources (travel, accommodation, etc.)
				• Strong support person
				• A physician committed to assisting with ongoing care

Absolute Contraindications	• Neoplasia • Chronic infections • Renal impairment • Pregnancy (current or planning)	• Active or current malignancy • Active fungal, viral or bacterial infections • Severe IHD or LVF • Severe respiratory conditions (e.g. end stage COPD) • Untreatable AAA • Severe occlusive ileac disease (since that's where the new kidney will be attached) • Physical abnormality preventing urine drainage	• Uncontrolled infection • Malignancy • Uncorrectable cardiopulmonary disease, brain damage • Active substance abuse • Non-compliance • Advanced age: may be a relative contraindication • HIV • Anatomical abnormalities	• Untreatable life-threatening illness, including malignancy • HIV positive • Hepatitis B positive with active hepatitis • Active substance abuse • Inability to abstain from tobacco • Severe emotional instability or severe psychiatric illness • Contraindications for immune suppressive therapy •
Relative contraindications		• Active gangrene (may indicated PAD) • Active peptic ulcer • Recurrent atherothrombotic events requiring antithrombotic treatment (e.g. stroke, clots, DVTs since the transplant procedure is high clot risk) • Current substance abuse (within 6 months) • Non-adherence to medications (within 6 months) • Severe PAD • Obesity		• BMI < 17kg/m^2 or > 30kg/m^2 • Physiologic age > 65 • Psychological/social instability • Intrinsic renal disease • Significant peripheral disease • Impaired left heart function (unless candidate for heart/lung transplant) • Symptomatic osteoporosis • Severe chest wall deformity • Sputum with fungus or pan-resistant bacteria • Hepatitis B or C infection

		• Limited life expectancy (it takes 3.5 years on average to find it, not worth it to list someone with a 1 year life expectancy)		• Liver cirrhosis
Listing Criteria			Patients who require a liver transplant (according to MELD score) and who have no contraindications receive a listing. Listing 1: Home Listing 2: Hospital Listing 3: ICU Listing 4: ICU, intubated Listing 4F: ICU, intubated, fulminant	Status 0: Accepted for transplantation, but currently inactive on wait list Status 1: Active on waiting list, but stable Active 2: Active on waiting list, but rapidly deteriorating

Donor Information	Deceased donors - entire pancreas used
	
	Older and heavier donors are ideal
	
	Process done ASAP to maximize number of platelets
		Deceased or living donors can be used	Cadaveric
			• Whole liver
			• Split liver
			  ○ Adult: segments 4-8
			  ○ Pediatric: segments 2-3
			Living Related Donor (50% of liver)
			• Advantages
			  ○ Increased donor pool
			  ○ Shorter wait times
			  ○ Scheduled procedures = short cold ischemic times
			• Disadvantages
			  ○ Graft survival may be slightly lower because the patient is receiving only half of a liver
			  ○ Complications to donor
			  ○ Outcomes worse if severely decompensated liver disease
				Can be a single lung (living donor) or double lung (decreased donor)
				
				Ideal characteristics
				• Healthy lungs (absence of disease, absence of trauma, < 72 hours of intubation, no smoking for last 15-20+ years)
				• ≤ 55 years old
				• Good perfusion (PaO2 > 300mmHg)
				• Clear chest x-ray and bronchoscopy

Donor-Recipient Matching	ABO compatibility Cross-matching Donor Considerations	Usually thorough (ABO, HLA, Antibody) since there are more donors and living donors.		ABO blood group Size matching (proper height, weight, chest circumference) • Need lung to fit into recipient chest • May be trimmed if needed

				No cross-matching (no time due to short ischemic time)

Medications

Induction Therapy

Alemtuzumab (30mg) daily OR Thymoglobulin (6mg/kg) OR Basiliximab (20mg) + etanercept (50mg on day 0, then 25mg days 3, 7, 10)
 	
Anticoagulation (enoxaparin) also initiated to prevent clotting around islets within liver (~2 weeks)
 	
Insulin initiated as well to give islets time to establish (usually about a month)
	Basiliximab OR
	ATGAM/alemtuzumab for patients at higher risk of rejection
		Anti-lymphocyte and anti-thymocyte globulins are rarely used
		• Since rejection of a transplanted liver is less common (compared to rejection of other organs)
		Anti-IL-2Rα more common
		• Good for:
		  ○ Steroid avoidance
		  ○ CNI delay and reduction
		• Minimal immune suppression protocols (tolerance)
		  ○ Reduces risk of recurrent hepatitis C
			Any of the following:
			• Daclizumab 2mg/kg on day 1-3, then 1mg/kg thereafter
			• ATGAM 10mg/kg IV infusion over 24 hours for days 1-7 until CNI doses are therapeutic
			• rATG 1.5mg/kg infusion over 6 hours daily for 3-5 days
			Exceptions to induction therapy
			• Hep C positive patients receiving Hep C positive organ
			• Colonization with MDR organisms

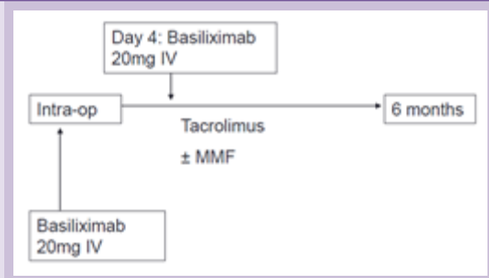
Maintenance Therapy

Tacrolimus (8-10ng/mL) + mycophenolate mofetil 1000mg BID
Insulin may be continued if islets are not able to maintain blood glucose levels on their own
	Reference: SYMPHONY study
	• Initially: CNI + antiproliferative agent (azathioprine or MMF) with or without CCS
	Calcineurin Inhibitor
	• Tacrolimus recommended as first line CNI; trough of 3-7ng/mL
	• Start CNI before or at time of transplant, there is no evidence that delaying introduction prevents delayed graft function.
	• After 2-4 months, use lowest dose of CNI since at this point the immune system adapts. Similar survival rates with high and low dose CNIs.
	• Monitor q2days post-transplant until target levels reached
		Typically CNI + mycophenolate mofetil
		• Discontinue MMF after 1 year
		• Cochrane Review measuring mortality and graft loss found that tacrolimus showed (in comparison to cyclosporine):
		  ○ Decreased acute rejection
		  ○ Decreased steroid resistant rejection
		  ○ Increased diabetes
		
		University of Alberta protocol: Give basiliximab 20 mg intravenously at the time of operation and again on Day 4 post-op. Start tacrolimus (with or without MMF) about Day 7 post-op.
			Calcineurin Inhibitor

Time Post-Transplant	Tacrolimus	Cyclosporine
0-6 months	12-15µg/L	350-400µg/L
6-12 months	10-15µg/L	300-350µg/L
1-5 years	5-10µg/L	~200µg/L
> 5 years	5-8µg/L	150-200µg/L

Antimetabolite
- Mycophenolate mofetil 1500mg PO/IV BID
- Azathioprine 2mg/kg PO daily

Steroids
- Methylprednisolone 2mg/kg IV BID for 3 doses, then
- Prednisone 1mg/kg PO daily, tapering up to 30mg/day by day 30, and then slowly tapering down over time as risk of rejection decreases

		<table><tr><th>Post-Transplant</th><th>Tacrolimus</th><th>Cyclosporine</th></tr><tr><td>0-1 months</td><td>6-9µg/L</td><td>300-350µg/L</td></tr><tr><td>1-3 months</td><td>6-9µg/L</td><td>300-350µg/L</td></tr><tr><td>3-6 years</td><td>5-7µg/L</td><td>200-250µg/L</td></tr><tr><td>6-12 months</td><td>5-7µg/L</td><td>140-200µg/L</td></tr><tr><td>>1 year</td><td>4-6µg/L</td><td>100-125µg/L</td></tr></table>Do not memorize Antiproliferative agent • MMF recommended Corticosteroid • Can discontinue during first week for low mismatch risk patients • If used beyond the first week after transplant, continue use since meta-analysis showed increased risk of rejection. mTORi agents • Delay introduction until graft functioning and surgical wounds healed. • In general, no good evidence for their use in renal transplants. • Also significant short and long term SEs. • Avoid if possible ** Consider reducing doses in EBV - recipient patients due to higher risk of PTLD		
Rescue Therapy		First Line • IV methylprednisolone 250-500g daily for 3 days • Restart oral prednisone if discontinued Other Options • Plasmapheresis • IV immunoglobulin • Rituximab (anti-CD20 antibody) • ATGAM/rATG (lymphocyte depleting antibodies)	Based on baseline immunosuppression • Switching to a more potent agent e.g. changing sirolimus to tacrolimus instead • Introduce an additional agent Pulse boluses of IV corticosteroids Anti-thymocyte or anti-lymphocyte antibody	Uncomplicated acute rejection • Methylprednisolone 500-1000mg IV daily for 3-5 days • Followed by prednisone taper over the ensuing 2-3 weeks Refractory Acute Rejection & Chronic Rejection • If applicable, switch from cyclosporine to tacrolimus Use of ATG therapy if needed

		• If not taking MMF, start • If taking azathioprine, switch to MMF If no response to above therapies, biopsy to investigate • BK nephropathy • Additional rejection • Other causes		
Infectious Prophylaxis and Treatment				

Pneumocystis Pneumonia (PCP)	Prophylaxis
	• Sulfamethoxazole-trimethoprim 400/80mg PO daily for 6 months
	• If sulfa allergy: pentamidine 300mg inhaled monthly
		Etiology
		• Infection with *Pneumocystis jiroveci*
		• Common fungal infection of the lung (75% seropositive)
		• Can cause severe, life threatening pneumonia in immunocompromised patients
		Diagnosis
		• Bronchiolar-lavage (BAL)
		• Lung biopsy
		Prophylaxis
		• Sulfamethoxazole-trimethoprim for 6 months, OR
		• Pentamidine 300mg inhaled monthly
		  ○ If sulfa allergy present
		  ○ Must be given in hospital
		• Dapsone 100mg + Levofloxacin 250mg daily
		Treatment
		• IV Septra (SMP/TMX)
		• IV CCS (for patients with PO2 of 70mmHg or less)
		• Reduce immunosuppressive agents
			Prophylaxis
			• Sulfamethoxazole-trimethoprim for 6 months, OR
			• Pentamidine 300mg inhaled monthly
			  ○ If sulfa allergy present
			  ○ Must be given in hospital
				Etiology & Epidemiology
				• Infection with *Pneumocystis jiroveci*
				• Common fungal infection of the lung (75% seropositive)
				• Can cause severe, life threatening pneumonia in immunocompromised patients
				Risk Factors
				• Immunosuppressive therapies
				• CMV infection
				• Episodes of rejection
				• Neutropenia
				• Low CD4+ T cell counts
				Prophylaxis
				• Life-long prophylaxis (due to high risk of infection in lungs)
				• First Line:
				  ○ Sulfamethoxazole/Trimethoprim 400/80mg or 800/160mg daily or three times weekly
				• Second Line
				  ○ Dapsone 50-100mg PO daily
				  ○ Atorvaquone 1500mg daily
				  ○ Pentamide 300mg inhaled via nebulizer every 3-4 weeks
				  ○ Clindamycin 300mg + 15mg pyrimethamine daily or three times weekly

Cytomegalovirus (CMV)	Prophylaxis • CMV prophylaxis done for 14 weeks regardless of CMV D/R status (valganciclovir 900mg BID)	Prophylaxis • Standard protocol (see attached) Treatment • Severe: IV ganciclovir • Mild: IV ganciclovir or PO valganciclovir • Continue until CMV no longer detectable by qPCR or immunoassay	Prophylaxis • Standard protocol (see attached)	Etiology & Epidemiology • Infection by cytomegalovirus (HSV-5) • Seroprevalence = 30-97% • Prevalence of infections ≈ 60% Risk Factors • D+/R- • Immunosuppression ○ Especially ALA antibodies • Concomitant infections • Neutropenia • Lung, small intestine, pancreas transplants Prophylaxis • Standard protocol (see attached) • Monitor CMV PCR weekly for 8 weeks following course of treatment Treatment • Ganciclovir 5mg/kg BID or valganciclovir 900mg BID until resolution • Patient may warrant a course of prophylaxis following resolution • Monitor CMV PCR weekly for 8 weeks following course of treatment
Aspergillus		Etiology • Ubiquitous inhaled fungal organism • Can cause IgE mediated infection with pulmonary infiltrate and cough, Treat as asthma (CCS) • Tracheobronchitis aspergilloma -> serious, causes vascular necrosis in the lung, can disseminate to the brain, heart and liver Prophylaxis • Voriconazole (best PO choice) • Can also consider itraconazole, posiconazole or amphotericin B (last line,		Etiology & Epidemiology • Ubiquitous mold in the environment • Infection prevalence ≈ 4-23.3% Risk Factors • Single lung transplant • Early airway ischemia • CMV infection • Rejection with augmented immunosuppression • Pre-transplant colonization • Post-transplant colonization within 1 year • Acquired hypogammaglobulinemia Other Factors

		use emulsion if necessary)		• Lung transplants most at risk due to constant exposure and reduced defense responses (e.g. mucociliary system) Prophylaxis • Amphotericin B 6mg inhaled Q8H or 25mg daily • Abelcet 50mg inhaled daily • Ambisome 25mg inhaled daily • Voriconazole 200mg PO BID • Itraconazole 200mg PO BID Treatment • As per prophylaxis for approximately 3 months depending on if infection resolve
Candida	Treatment • Nystatin 5mL swish and swallow	Etiology • Common normal flora that can infect skin, throat, vagina in immunocompromised patients • Severe disease: esophagitis, pneumonia, septicemia Prophylaxis • Oral clotrimazole lozenges or nystatin swish and swallow or fluconazole for 1-3 months after transplant • As above 1 month after anti-thymocyte treatment	Treatment • Nystatin 5mL swish and swallow QID • Fluconazole 200mg daily (if high risk)	Treatment • Nystatin 5mL swish and swallowed QID
Transplant Specific Infections		<u>BK Polyomavirus</u> Etiology • 90% of population seropositive with latent virus in renal tubules • May reactivate in immunocompromised patients can cause PyVAN (Polyomavirus Associated Nephropathy) Monitoring (qPCR) • Monthly for first 3-6 months post-transplant • Every 3 months until 12 months post-	<u>Hepatitis B (Recipient HBsAg +)</u> Treatment • HepaGam 35mg IV ○ Administer during anhepatic phase (in operating room) • Post-Op ○ HepaGam 5mL IV daily for 1 week ○ Then HepaGam 5mL IV weekly for 4 weeks ○ Anti-HBS titres twice weekly (starting day 5 post-op)	

transplant
- Anytime there is an unexplained rise in SCr

Treatment
- Reduce doses of CNI and antiproliferative for patients with more than 10000 copies of BKV/mL
- Reduce CNI by 20-50%
- Reduce MMF by 50%. D/C if needed and switch to leflunamidine
- IV Codifovir at 1-3 week intervals
- IvIG 0.2-2g/kg

<u>HSV-1 & HSV-2</u>

Etiology
- Common viral infection
- Highest reactivation 1 month post-transplant (due to most intense immunosuppression)

Prophylaxis
- Ganciclovir or valacyclovir (unless patient taking valganciclovir in which case they have sufficient antiviral protection)

Treatment
- PO acyclovir or valacyclovir or famciclovir
- Systemic should be treated with IV acyclovir

<u>Varicella Zoster</u>

Etiology
- Common childhood viral infection
- May reactivate as shingles
- Can cause disseminated infection which is life threatening

Treatment
- VZIG (varicella zoster immunoglobulin) within 96 hours of exposure to active
    - Anti-HBS titre target > 500
  - Nucleoside analogue
    - Lamivudine
    - Entecavir
    - Tenofovir

<u>Recurrent Hepatitis C</u>

Prevalence
- Virus recurs in almost all patients
- 25-35% in 5 years

Management
- INF-α ± ribavirin
  - INF alone = 15% Sustained Viral Response (SVR)
  - INF + ribavirin = 45% SVR
- PEG-Interferon + Ribavirin
  - Further increased SVR

Predictors of Response
- HCV Genotype
  - Types 2 or 3 - SVR = 80% in 24 weeks (INF + Ribavirin)
  - Type 1 - SVR = 33% in 48 weeks (INF + Ribavirin)
  - Type 1 - SVR = 40-45% in 48 weeks (PEG-INF + Ribavirin)
- Viral load
- Adherence

		infection • If window of VZIG is passed, 7 day course of PO acyclovir <u>E. Coli</u> All patients at high risk of UTI with *E. col*i, treat with sulfamethoxazole/trimethoprim <u>Others</u> Tuberculosis, Hepatitis B or, HIV		
General Considerations				
Malignancy		Prevalence • 3-5x higher than normal population • By 10 years increased to 13.8x Risk Factors • Dose and duration of immunosuppression • Age • Cigarette smoking • Chronic viral infections		Prevalence • Malignancy ○ Year 1: 3.7% ○ Year 5: 12.4% ○ Year 10: 25% Risk Factors • Pre-transplant seronegative EBV status • High strength immunosuppression
Post-Transplant Lympho-proliferative Disorder (PTLD)		Prevalence • 1.2-10.1% • Mean time to PTLD = 32 months Risk factors • EBV Negative recipient, positive donor Treatment • Reduce or withdraw immunosuppression • Rituximab • Antiviral treatment • Surgery • Radiation therapy • Chemotherapy	Prevalence • Mean Onset: 10 months post-transplant Survival • Year 1 = 1 85% • Year 20 = 45% • Better survival if ○ Limited disease ○ Polymorphic/polyclonal disease ○ Child ○ Using tacrolimus Risk Factors • EBV negative: specifically if donor is EBV-positive • Steroid bolus • CMV disease • Blood products	Prevalence • 2-8% Presentation in lung transplant • Nodal involvement to disseminated involvement • Thorax (69-89%), abdomen (20-34%) • Mucosal tissue of GI tract, bronchial airway, skin Risk Factors • Pre-transplant seronegative EBV status • High strength immunosuppression Treatment • Rituximab • Decrease immunosuppression • Surgery • Radiation therapy

			• Excessive immunosuppression
			Management
			• Limited Disease (one site only)
			  ○ Surgical extirpation or localized radiation
			  ○ Minor/moderate immunosuppression reduction (25%)
			• Extensive Disease (more than 1 site)
			  ○ **Intense immunosuppression reduction (50%)**
			  ○ **Extirpation of local disease**
			  ○ **Rituximab**
			  ○ Chemotherapy for rituximab failure or poor prognosis
			  ○ If CNS involvement, radiation without chemotherapy
			• Critically Ill
			  ○ Stop all immunosuppression except prednisone
				• Chemotherapy

Renal Dysfunction		Etiology • CNI toxicity • Hypertension • Hyperlipidemia • Diabetes • Insults to kidney (e.g. AKI) Management • Decrease CNI dose/replace agent • Aggressively treat risk factors (hypertension, hyperlipidemia, diabetes) • ACEIs/ARBs to slow progression • Dialysis and renal transplant	Prevalence • 20% of patients have GFR < 30mL/min after 5 years Risk Factors • Prior existence/history • Peri-operative hemorrhage • Vascular clamping with hypotension • Nephrotoxic drugs • Sepsis • Shock • Graft dysfunction Management • Colloid-based hydrous replacement • Diuretics • Dopamine: to promote normal kidney function • Noradrenaline • Dialysis	Prevalence • 25.5% at year 1 • 37.8% at year 5 Etiology • CNI toxicity • Hypertension • Hyperlipidemia • Diabetes • Insults to kidney (e.g. AKI) Management • Decrease CNI dose/replace agent • Aggressively treat risk factors (hypertension, hyperlipidemia, diabetes) • ACEIs/ARBs to slow progression • Dialysis and renal transplant

Diabetes		Risk Factors
		• Glucocorticoid use
		  ○ Especially in patients with frequent episodes of rejection requiring high dose steroids
		• CNI use (tacrolimus > cyclosporine)
		• Older age
		• Obesity (BMI > 30m/kg^2)
		• Hepatitis C infection
		Management
		• Insulin
		• Oral hypoglycemics
			Prevalence
			• 4-20%
			Risk Factors
			• Obesity
			• HCV infection
			• Immunosuppression
			• Interferon-γ prior to transplant
			• Gestational diabetes history
			Management
			• Insulin
			• Oral hypoglycemics
				Prevalence
				• Year 1: 24.3% of patients
				• Year 5: 33.5% of patients
				Risk Factors
				• Glucocorticoid use
				  ○ Especially in patients with frequent episodes of rejection requiring high dose steroids
				• CNI use (tacrolimus > cyclosporine)
				• Older age
				• Obesity (BMI > 30m/kg^2)

Hypertension		Prevalence
		• > 90% of CNI treated patients
		Etiology & Risk Factors
		• Immunosuppressive Agents
		Management
		• As per hypertension guidelines
			Prevalence
			• 50-70% first few months
			• Less frequent and later if on tacrolimus
			Management
			• Reduce CNI dose
			• Early steroid withdrawal within the first 3-6 months
			• CCBs e.g. diltiazem, amlodipine
			  ○ Helps manage HTN
			  ○ Drug interaction with tacrolimus: reduces breakdown of tacrolimus
			  • Allows us to give less tacrolimus to produce the same effect
			• ACEIs
			  ○ Helps protect kidneys as well as manage HTN
			• Loop diuretics
			  ○ Reduces edema; promotes elimination of toxins
				Etiology & Risk Factors
				• Immunosuppressive Agents
				Prevalence
				• Year 1: 51.9%
				• Year 5: 85.6%
				Management
				• As per hypertension guidelines

Dyslipidemia		Prevalence • > 80% of patients Etiology & Risk Factors • Immunosuppressive agents Management	Prevalence • 17-66% develop Risks • Diet • Genetic predisposition	Prevalence • Year 1: 20.5% • Year 5: 52.2% Etiology & Risk Factors • Immunosuppressive agents

		• As per dyslipidemia guidelines (e.g. statin therapy first line)	• *de novo* predisposition
			• Post-transplantation kidney dysfunction
			• Immunosuppressive treatment
			Management
			• Diet
			• Weight reduction
			• Strict control of DM
			• Arterial hypertension management
			• Smoking or drinking cessation
			• HMG-CoA reductase inhibitors
			  ○ Start low, titrate up
			  ○ Some interactions between statins and immune suppressants
			  • Cyclosporine causes rosuvastatin levels to increase dramatically, which can lead to rhabdomyolysis à avoid giving rosuvastatin with cyclosporine
				Management
				• As per dyslipidemia guidelines (e.g. statin therapy first line)
				• NB: targets are controversial in this population

Osteoporosis		Prevalence
		• 5-11% fracture rate
		Risk factors
		• Metabolic bone disease
		  ○ Patients often already have it prior to transplant, worsened by prednisone
		• Amenorrhea
		• Hypogonadism
		• Immune suppression
		• Chronic heparin expression
		Management
		• Calcium 1000mg daily + vitamin D 800mg IU daily
		• Regular weight bearing exercise
		• Estrogen & hormone replacement therapy
		  ○ Be aware that transplant patients at increased risk of
			Prevalence
			• 20% of livers have atraumatic bone fractures
			• Increases to 65% if cholestatic disease or re-transplant
			Risks
			• Hormonal changes of liver disease
			• Prolonged immobilization
			• Immunosuppressive treatment
			Management
			• Calcium
			• Vitamin D
			• Calcitonin
			• Bisphosphonates
				Prevalence
				• Year 1: 6-18% fracture rate
				Risk factors
				• Low exercise (common in lung transplants)
				• Prior glucocorticoid use (common in lung transplants, e.g. prednisone for asthmatics or COPD patients)
				• CF patients already at risk due to malabsorption
				• Drug
				  ○ Corticosteroids
				  ○ Immunosuppressive agents
				Management
				• Calcium 1000mg daily + vitamin D 800mg IU daily
				• Regular weight bearing exercise
				• Estrogen & hormone replacement therapy

		thromboembolisms • Calcitriol • Bisphosphonate therapy		○ Be aware that transplant patients at increased risk of thromboembolisms • Calcitriol • Bisphosphonate therapy
Organ-Specific Considerations				
	Not all transplants will remove need for insulin, but overall it will reduce the need for insulin and patients tend to have less labile blood glucose levels Transplants have been shown to reduce morbidity commonly associated with diabetes (retinopathy, neuropathy, etc.)	<u>Orthotopic Transplant</u> • Kidneys left in place most of the time, vasculature and ureter re-routed to new kidney inserted in the iliac fossa • Kidneys only removed in cases of cancer or hypertension <u>Complications of Rejection</u> Management of acute rejection is critical, since even a slight dip in renal function results in high graft loss • e.g. dropping to 75% of pre-rejection renal function leads to graft loss in 45% of patients! Main risk factors for acute rejection: • # of HLA mismatches • Older age of donor • Younger recipient age • PRA antigens • Donor specific antibodies • ABO incompatibility • Delayed graft function Must be diagnosed by biopsy <u>Success of Kidney Transplants</u> Kidney transplants are some of the most successful and beneficial • One of the best survival rates partly due to ability to use living donors and do better matching	<u>Primary Graft Failure</u> Poor liver function to maintain the individual's life leading to death or re-transplantation during the first seven post-operative days • A functioning liver is required to sustain life • If primary graft failure occurs, the patient will require a new liver within a week of the operation Prevalence • 5-10% Risk Factors • Advanced age • Hemodynamic instability • Suboptimal donors • Cold ischemia time: liver kept on ice for a long time • Reperfusion damage: new/return of blood flow damages the organ • Release of intestinal endotoxin • Drug-related liver toxicity: e.g. acetaminophen overdose <u>Special Protocols</u> Tumour Protocol • Sirolimus ± Tacrolimus ○ Since sirolimus helps prevent DNA replication of the tumour ○ Increased recurrence-free survival rates	<u>Diaphragm Paralysis</u> • Occurs due to phrenic nerve damage • Longer ICU & hospital stays • Reduced lung capacity and forced vital capacity • Limited exercise capability • Ventilatory failure <u>Esophageal Dysmotility</u> • Occurs due to vagus nerve injury • Delays gastric emptying • Risk of chronic aspiration, pulmonary sequelae, and increased risk of allograft dysfunction • Treatment ○ Laparoscopic fundoplication ○ TENS ○ Pro-motility agents (metoclopramide, domperidone) ○ PPIs or H_2RAs <u>Bronchiolitis Obliterans</u> • Most significant long-term cause of morbidity and mortality (50-60% of patients by year 5) • Results in chronic allograft dysfunction, injury and inflammation of small airways (resulting in fibrosis) • Prevention/Treatment ○ Augmented immune suppression

- Deceased donors most common but many living donations done as well
- In some cases family members or the LDPE can find suitable matches

- Higher survival than dialysis, lower health care costs
- Transplant BEFORE dialysis makes more sense for the patient, much less difficult and better prognosis
  - Better QoL for patient and health care savings too.

Immediately after transplant the kidney may need time to rest, if so dialysis may be performed for a short time

- Increased patient survival rates at 1, 3, and 5 years

Nephrotoxicity

- Sirolimus ± low dose tacrolimus or mycophenolate mofetil

Neurotoxicity

- Sirolimus ± mycophenolate mofetil

Tacrolimus & Sirolimus concentration

	Tacrolimus	Sirolimus
< 12 months	8-12µg/L	10-12µg/L
> 12 months	5-8µg/L	6-8µg/L
> 2 years (infection or renal dysfunction)	3-5µg/L	6-8µg/L

- Hepatocellular carcinoma patients may have lower targets

<u>Hepatic Artery Thrombosis</u>

Prevalence

- 1.5-25%

Complications

- If the clot occurs early on → ischemia/necrosis of graft
- If the clot occurs later → biliary complications (↓ bile flow due to inadequate blood perfusion)
- Hypercoagulability: due to decreased production of anti-coagulation factors by the liver
- 50-70% of patients require re-transplantation
  - If the clot occurs during the transplant, a new liver is required immediately

Etiology

- Poor arterial flow
- Increased sinusoidal resistance
- Preservation injury: if the liver was damaged from being put on ice

- Total lymphoid irradiation
- Re-transplantation
- Early fundoplication

- Stenosis of the anastomies: attachment by suture could cause narrowing of area, resulting in ↑ pressure and turbulence

Prevention

- ASA 80mg daily indefinitely
  - For clot prevention (antiplatelet)
- Unfractionated heparin infusion: bridging therapy from OR to several days afterward
  - To ensure the veins stay open

<u>Portal Vein Thrombosis</u>

Prevalence

- 2-3%

Risk Factors

- Pre-transplantation portal thrombosis
- Splenectomy
- Prior portal hypertension surgery

Prevention

- Aspirin 80mg daily
- Unfractionated heparin infusion

<u>Monitoring Liver Function</u>

Liver enzyme dysfunction should improve after transplant

- Elevated AST/ALT should decrease by 50%/day
- Elevated bilirubin should improve
- Elevated INRs should improve
- Signs/symptoms of liver failure should resolve (e.g. encephalopathy)