

Post-Transplant Care for the Community Provider

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The Liver Transplant Continuum

- Picking a candidate
- Referral
- Evaluation
- Listing
- Transplant
- Follow up



Liver Transplant Surgery

- Deceased donor (DDLT) vs. Living Donor (LDLT)
- Brain death vs. DCD
- Usually 6-8 hours
 - Can be up to 12
- Hockey stick incision
- ICU → Floor → D/C
 - 7-10 days barring any complications

Surgical Complications

- Hepatic artery thrombosis
 - Risk doubles for LDLT
 - Another emergent transplant may be necessary
- Portal vein thrombosis
 - May or may not require re-transplant
- Biliary complications
 - Leak: 7.8% DDLT, 9.5% LDLT
 - Risk of stricture: 20% in LDLT
- Bleeding
 - 10% of recipients require a 2nd surgery for bleeding
- Infection
 - Lifelong risk

Post-Liver Transplant Timeline

0-12 Months

Managed closely by transplant center

- Immunosuppression management with frequent adjustments
- Labs every 2-4 weeks
- Frequent visits with the transplant team

1-5 Years

Transitioning back to local care

- Importance of PCP/local GI
- More stable doses of immunosuppression
- Labs every 3-6 months
- Visits with transplant hepatology every 6-12 months

>5 Years

Majority of care by local providers

- Very rare adjustments to immunosuppression
- Labs every 6-12 months
- Annual visits with transplant

Most Common Complications

- Acute or chronic rejection
- Biliary stricture
- Recurrence of primary liver disease (HBV, MASH, PSC, PBC, AIH, etc.)
- Infection
- Complications associated with immunosuppression
 - Renal insufficiency
 - Metabolic syndrome: HTN, HLD, DM, obesity
 - Gout
 - Bone disease
 - Malignancy

Post-Liver Transplant Complication Timeline

0-12 Months

Rejection
Bacterial infection
Biliary leak/stricture
Vascular complications
Immunosuppression side effects/toxicity
Nephrotoxicity

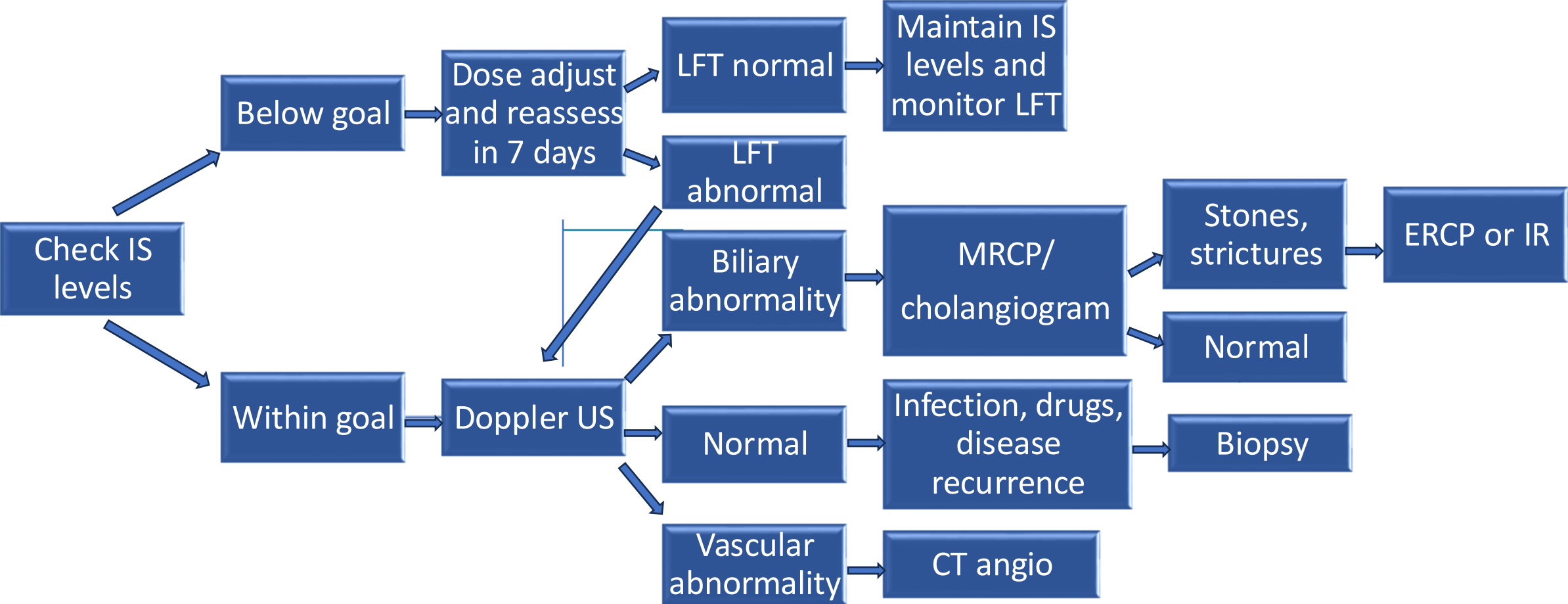
1-5 Years

CMV
Biliary stricture
Recurrent disease
Diabetes
Immunosuppression side effects
Nephrotoxicity

>5 Years

Cancer
Cardiovascular disease
Diabetes
Recurrent disease
Immunosuppression side effects
Nephrotoxicity

Evaluation of Abnormal Liver Tests Post-LT



Liver Transplant Rejection

	EARLY ACUTE	LATE ACUTE	CHRONIC
TIMING	1-90 days	>90 days	Months to years
INCIDENCE	20%-40%	20%-40%	< 2%
PRESENTATION	Asymptomatic, elevated LFT	Asymptomatic, elevated LFT	Elevated LFT, jaundice
DIFFERENTIAL	Biliary obstruction, reperfusion injury	Autoimmune hepatitis (recurrent or de novo), viral hepatitis	Recurrent PBC, PSC
OUTCOME	Reversible	Reversible	Irreversible

- Can only be diagnosed histologically
- Cellular rejection
- Ductopenic rejection (vanishing bile duct syndrome)

Immunosuppression

Immunosuppressant	Trade Names	Class	Typical Dose	Typical Plasma Level	Side Effects
Tacrolimus	Prograf Astagraf, Envarsus	Calcineurin inhibitor	1-10 mg q 12 h 5-15 mg daily	5-10 mg/mL	Nephrotoxicity Neurotoxicity Diabetes Hypertension
Cyclosporine	Neoral Gengraf Sandimmune	Calcineurin inhibitor	100-300 mg q 12 h	200-300 ng/mL	Nephrotoxicity Neurotoxicity Diabetes Hypertension Gingival hyperplasia hirsutism
Mycophenolate mofetil	Cellcept Myfortic	Antimetabolite IMPDH inhibitor	1000-1500 mg bid Or 360-720 mg bid	5-10 ng/mL	GI side effects Leukopenia
Everolimus	Zortress	mTOR inhibitor	0.5-5 mg q 12 h	5-10 ng/mL	Anemia Proteinuria Hyperlipidemia Pulmonary toxicity
Sirolimus	Rapamune	mTOR inhibitor	1-5 mg daily	5-10 ng/mL	Anemia Proteinuria Hyperlipidemia Pulmonary toxicity

IMPDH indicates inosine monophosphate dehydrogenase inhibitor; mTOR, mammalian target of rapamycin.

*****Titration of immunosuppression will almost exclusively remain with the transplant center*****

Diet After Liver Transplant

- Avoid

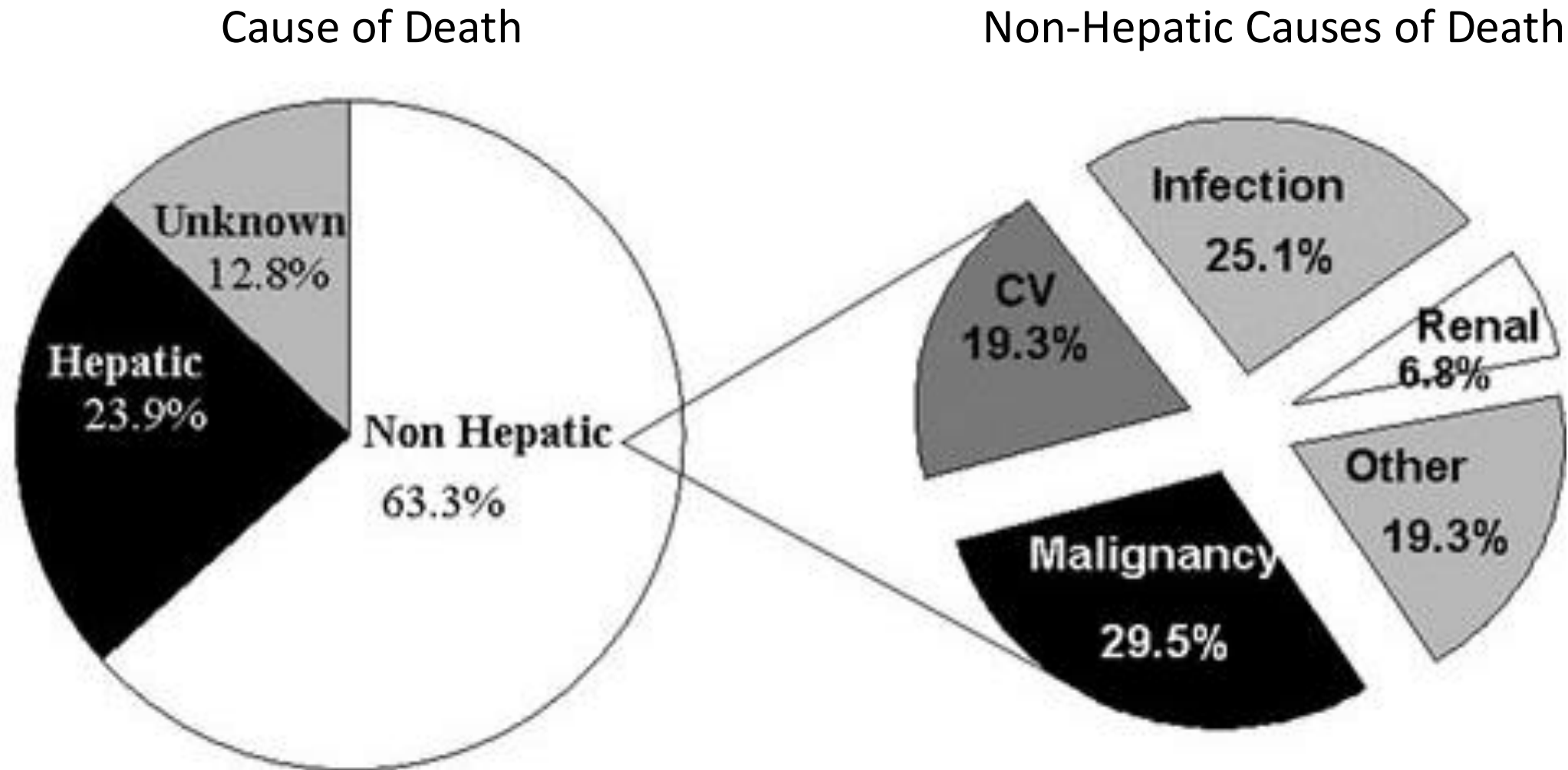
- Grapefruit
- Pomegranate
- Raw or undercooked meats, seafood, eggs, etc.
- Herbal supplements, especially
 - St. John's Wort
 - Vitamin C
 - Ginseng
 - Echinacea
 - Ashwagandha
 - Garcinia cambogia
 - Green tea extract
 - Turmeric
 - Black cohosh
 - Boron Avenov

- Hydration!
- Low salt, low fat diet
- May need low potassium diet
- May need extra calcium and Vitamin D
- Avoid alcohol

Post-LT Disease Recurrence & Considerations

MASH	Healthy weight, GLP-1, bariatric surgery
HBV	Post-LT prophylaxis
PBC	TSH and bone density; ursodiol
PSC w/ IBD	Annual CSP with biopsies, colectomy?
AIH	Long-term low dose steroids?
ETOH	Relapse prevention programs, Peth

Long-Term Mortality After Liver Transplantation



Mitigating Risk

Mitigating Cardiovascular Risk

- Hyperlipidemia
 - Statins are ok!
 - Pravastatin preferred but atorvastatin may be needed
 - Avoid cholestyramine – can impair absorption of CNIs
- DM
 - Usually on insulin early post-op (PTDM)
 - May need to avoid metformin
 - Steroid-free IS regimen
 - GLP-1s
- HTN
 - Use beta blockers or calcium channel blockers
 - Avoid ACEs and ARBs due to hyperkalemia
 - Diuretics not used as primary therapy

Mitigating Renal Disease

- Cause of renal disease is multifactorial
 - Pre-existing CKD or renal failure prior to LT
 - ATN during LT
 - CNI toxicity
 - DM & HTN

- CNI dose reduction
- Control HTN and DM
- Avoid nephrotoxic drugs
- Avoid NSAIDs
 - Acetaminophen OK up to 2g daily

Mitigating Bone Disease

- DEXA scan
 - Yearly for osteopenic patients
 - Every 2-3 years for patients with normal BMD
- Osteopenia
 - Weight-bearing exercise
 - Calcium + Vitamin D supplements
- Osteoporosis
 - Bisphosphonates are ok!
 - New SubQ agents

Mitigating Infection

- Hand washing
- Avoid public places
- Wear a mask
- Consume filtered water
 - Avoid river and lake water
- Avoid high-risk pets such as birds, rodents, snakes & chickens
- Use precautions against ticks and mosquitos
- Avoid unpasteurized foods as well as raw/undercooked meat & eggs
- Review travel plans with healthcare provider

Infections

Post operative GNR and multi-drug resistant GNR

- Hospital acquired infection
- Bacterial wound infection
- Biliary sources
- DCD donor recipients at higher risk

3-6 months Opportunistic infection

- Herpes viruses (CMV, HSV, VZV, EBV)
- Fungal (*Aspergillus* and *Cryptococcus*)
- Nocardia, listeria, mycobacterium
- *P. jirovecii*

3-24 months Community acquired infection

- Intra-abdominal and lower respiratory tract
- Strep pneumonia
- Respiratory viruses

Infection Prophylaxis

ORGANISM	MEDICATION	DURATION	CONSIDERATIONS
CMV <ul style="list-style-type: none"> • D+/R- • R+ 	<ul style="list-style-type: none"> • Valganciclovir 900 mg/day • Valganciclovir 900 mg/day or weekly CMV DNA and start if viremic 	<ul style="list-style-type: none"> • 3-6 months • 3 months 	Valganciclovir is not FDA approved for prophylaxis against CMV in OLT. It is approved for kidney and heart transplant.
<i>P. jirovecci</i>	Sulfamethoxazole-trimethoprim (single strength daily or double strength 3x/week) Dapsone 100 mg daily	6-12 months	Longer duration if on higher levels of immunosuppression. If myelosuppression, nephrotoxicity consider dapsone
Fungi	Fluconazole 100-400 mg/day	4-6 weeks	High risk patients only: Pre-LT fungal colonized, RRT, choledochojejunostomy

Post-LT Antimicrobials, Antivirals, & Antifungals

<u>DRUG</u>		<u>INTERACTION</u>			<u>CAUTIONS</u>
		TAC	SRL/EVR	MMF	
Antibiotics	Azithromycin	+/-	+/-	-	May ↑ IS levels if given concomitantly
	Ciprofloxacin	++	-	+	TAC= prolonged QTc; ↓ MMF levels
	Sulfonamides	++	++	+	Myelosuppression, nephrotoxicity (consider dapsone)
Antifungals	Fluconazole	++	++	-	↑ IS levels
Antivirals	Valganciclovir	-	++	+	Myelosuppression, ↑ MMF levels
	Tenofovir DF	++	-	+	Nephrotoxicity, tubular necrosis
	Tenofovir AF	-	-	-	
	Entecavir	-	-	-	

TAC= tacrolimus; SRL= sirolimus; EVR= everolimus; MMF= mycophenolate mofetil

Opportunistic Infections

- Cytomegalovirus (CMV)
 - Most common post OLT, especially in first 4 months
 - +/- at highest risk
 - “CMV mismatch”
 - Headaches, fever, fatigue, myalgia, pancytopenia, nausea, diarrhea
 - Treat aggressively – valganciclovir
 - CMV colitis, pneumonitis, hepatitis, nephritis, retinitis
- Epstein Barr Virus (EBV)
 - Post-transplant lymphoproliferative disease (PTLD)
 - Fever, malaise, night sweats, weight loss
 - Minimized immunosuppression
- *Pneumocystis jiroveci* (PJP)
 - Trimethoprim/sulfamethoxazole
 - Elevated K

Mitigating Post-LT Malignancies

- **NO SMOKING**
- **Mammo, pap, PSA, CT chest for former smokers**
- Increased incidence post-OLT require more intensive screening
 - Solid tumor (2-3-fold↑ over general population)
 - Skin cancer (10-30-fold ↑ over general population)
 - Usually, squamous cell or basal cell
 - Sunscreen - SPF 50+, Annual FSBE
 - Switch from CNI to mTOR/MMF
 - Post-Transplant Lymphoproliferative Disorder (PTLD)
 - EBV (R-/D+), OKT3, antithymocyte globulin, CYA, HCV
 - Treatment= CNI reduction/withdrawal; rituximab +/- chemotherapy
- Underlying liver disease may be associated with cancer!
 - PSC + UC → Colon cancer
 - Recurrent viral hepatitis → Hepatocellular carcinoma
 - ALD → oropharyngeal and esophageal squamous cell cancer

Vaccines

- Patients may “lose” immunity during the transplant process
- Common to wait 3-12 months post-OLT once maintenance immunosuppression levels have been achieved
 - During outbreak, flu can be given as early as 1 month post
 - COVID 19 vaccine
- High-dose vaccines to develop more robust immunity
- Need influenza, both pneumococcal vaccines
- No live vaccines ever
 - New shingles vaccine is ok!
- Household & close contacts need to also be vaccinated!
- Children receiving live virus vaccines
 - Shed virus in stool

Sex, Pregnancy & Reproduction

- Pre-transplant amenorrhea – fertility usually regained
- Avoid use of teratogenic immunosuppressants
 - 2 forms of reliable contraception
 - 1 in 4 children will have birth defect
 - 50% miscarriage
- Mycophenolate → Azathioprine
- Liver transplant follow up along with high-risk OB
- Male fertility can be affected by IS
- Male sexual dysfunction – sildenafil is OK

Key Takeaways

- Liver complications: Rejection & stricture
- Blood work needs “trough” immunosuppression level
- Ascites or elevated LFTs are never normal post-OLT
- Collaborate with the transplant center for all immunosuppressant changes and new medications
- Mycophenolate is bad in pregnancy
- Have a low threshold to screen for cancer and treat infection
- Mitigate cardiovascular risk
- Preserve renal function
- Don't forget the DEXA scan
- And lastly.....