

Post-Liver Transplant

Samantha Halpern, MSN, CRNP
Nurse Practitioner
Liver Transplant Surgery

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Objectives

- ◆ **Discuss post-liver transplant management after discharge**
- ◆ **Identify standard medication regimen in liver transplant recipients**
- ◆ **Review immunosuppression including function, drug class, and side effects**
- ◆ **Discuss ways to live healthy after transplant**
- ◆ **Describe potential postoperative complications, problems, and management**

What happens after discharge?

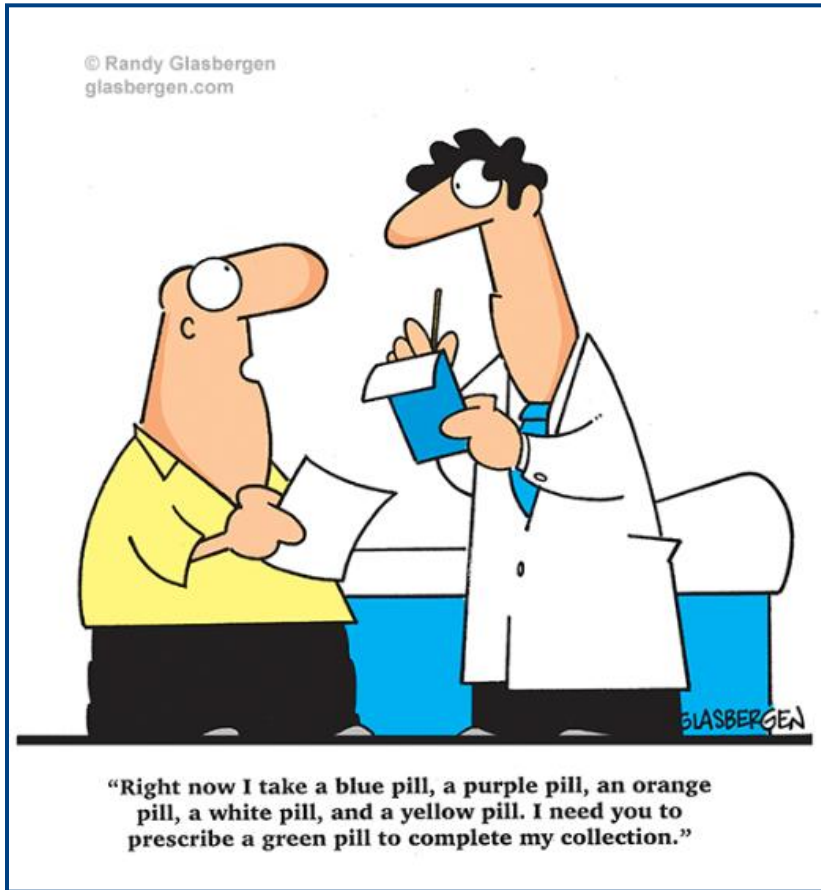
- ◆ 5 liver transplant (LT) NPs manage patients
- ◆ **Routine clinic appointments** in the post-transplant surgery clinic
 - Weekly for the first 1 month
 - Gradually space out visits afterwards
 - Staples removed around POD 21
- ◆ **Routine labs:**
 - Weekly labs for first 3 months
 - Gradually space out labs according to results
 - Increase frequency of labs if changing IS
- ◆ **Vital signs:**
 - Keep log daily and bring to office visits
- ◆ Transplant pharmacist, social worker, dietitian, surgeons always available



Liver Transplant Medications

- ◆ **Nystatin to prevent thrush**
 - Stopped at 3 months
 - ◆ **Acyclovir to prevent CMV**
 - Stopped at 3 months
 - ◆ **Ganciclovir to prevent CMV**
 - Donor CMV+, Recipient CMV-
 - Switch to oral Valganciclovir after 90 days
 - Daily infusions at home
 - ☹️ Low blood cell counts
 - ◆ **H2 Blocker or PPI to prevent GERD**
 - Can stop when prednisone is stopped
 - ◆ **Colace**
 - As needed
- ◆ **Other possible medications:**
 - Ursodiol
 - BP meds
 - Insulin
 - Magnesium
 - Lasix
 - Kayexalate/florinef
 - Aspirin
 - ◆ **OTC meds:**
 - Tylenol up to 2,000 mg daily
 - ◆ **NOT allowed to take:**
 - NSAIDs
 - Herbal supplements

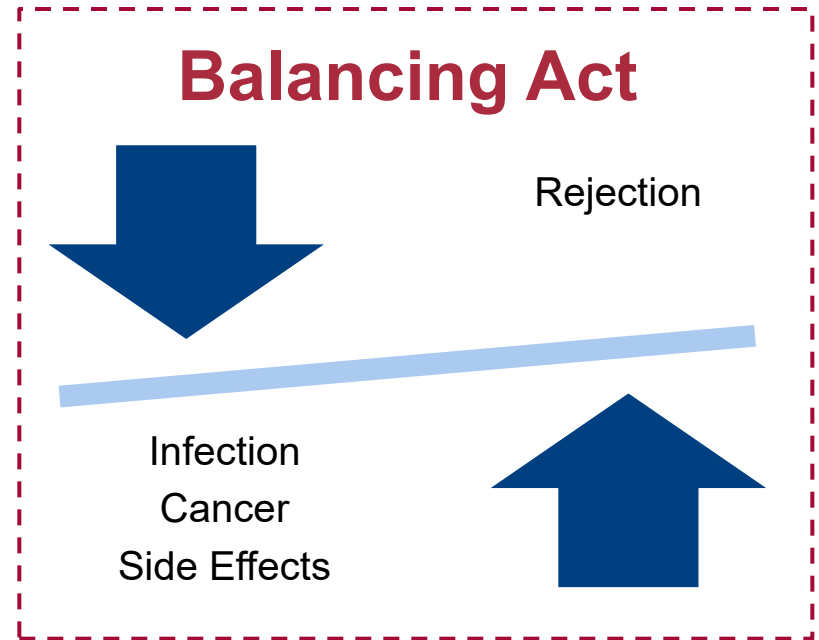
Immunosuppression (IS)



- ◆ Prevents immune system from attacking non-self
- ◆ Without IS, the recipient immune system will destroy the liver:
 - Rejection
 - Graft dysfunction
 - Graft loss/death
- ◆ Lifelong IS
- ◆ Increases risk for infection and cancer
- ◆ Monitor levels closely; can decrease levels in time
- ⊘ Running out is NOT an option

Immunosuppression

- ◆ The choice of IS depends on the following:
 - Indication for transplant
 - Comorbidities
 - Drug side effects
 - History or recurrent rejection
 - Prior IS agents
 - History of or risk for cancer/infection



UNWANTED SIDE EFFECTS OF IMMUNOSUPPRESSIVES				
SIDE EFFECT	CORTICOSTEROIDS	CNIs	mTOR INHIBITORS	MYCOPHENOLATE MOFETIL
Kidney injury	-	+++	+ (proteinuria)	-
Bone disease	+++	-	-	-
Gastrointestinal	+/-	-	-	+
Bone marrow suppression	-	-	-	+
Pulmonary fibrosis	-	-	+	-
Hypercholesterolemia	+	+	+++	-
Diabetes	++	+ (tacrolimus)	-	-
Hypertension	+	++	+	-

Immunosuppression

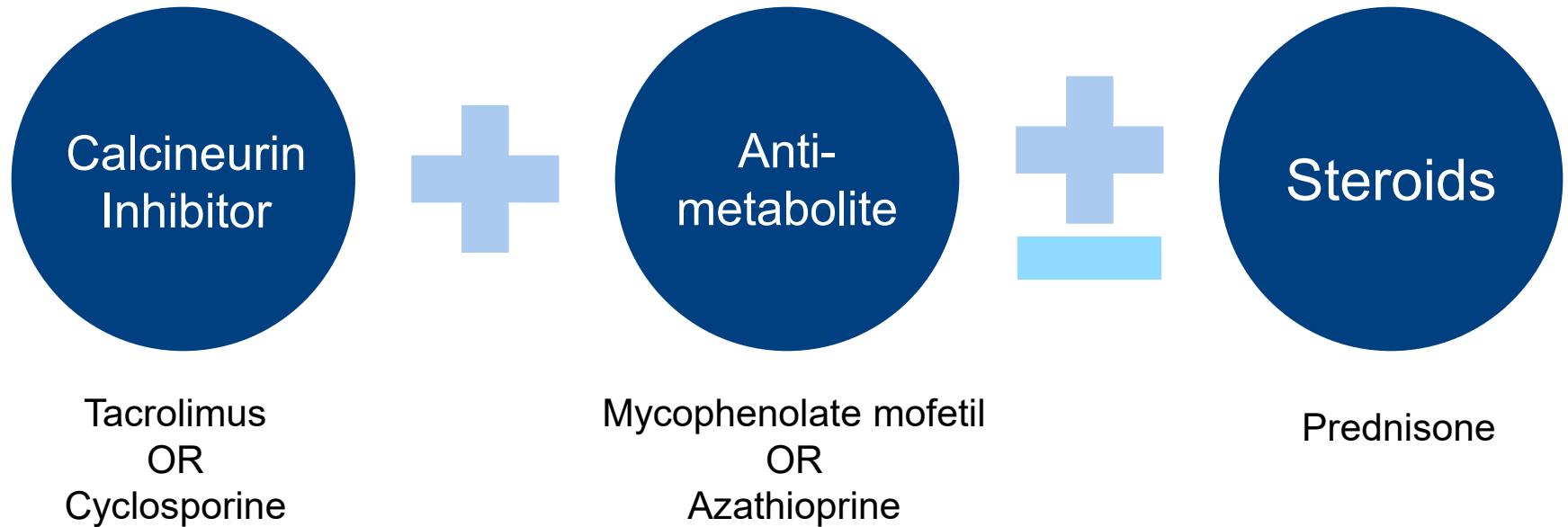
IS	Directives & Benefits	⊖ Potential Side Effects
Calcineurin Inhibitors (CNIs): Tacrolimus and Cyclosporine	Keep at lower level for renal dysfunction	kidney injury, electrolyte abnormalities, hyperglycemia, hypertension, hand tremors, hair loss, headaches, confusion/agitation
Glucocorticoids (Prednisone)	Taper off by 3-4 months except if PSC	diabetes, weight gain, mood swings, osteopenia, vision changes, trouble sleeping
mTOR inhibitors: Sirolimus and Everolimus	<ul style="list-style-type: none"> • Cannot start until at least 30 days post, poor wound healing • May preserve renal function • Anti-neoplastic 	proteinuria, hypercholesterolemia, mouth ulcers, interstitial lung disease, teratogenic
Antimetabolites: Azathioprine and Mycophenolate Mofetil	Help achieve lower tac level to spare kidneys	bone marrow suppression, diarrhea, nausea/vomiting, teratogenic

All meds prescribed by outside provider MUST be checked with transplant team:

Fluoroquinolones · Antifungals · Macrolides

⊖ No NSAIDs, herbal supplements, or grapefruit

Putting It All Together



Exception:

mTOR Inhibitors have been used in *replacement* of CNIs or in *replacement* of anti-metabolites

Promoting Health After Liver Transplant (1 of 3)

- ◆ **Hand washing**
- ◆ **No raw meat or raw seafood**
- ◆ **Avoid crowds**
- ◆ **No smoking/alcohol**
 - THC
- ◆ **Pets**
- ◆ **Safe travel**
- ◆ **Outdoors**
 - SPF 35+, insect repellent, DEET
 - Protective clothing
- ◆ **Activity:**
 - No heavy lifting >10 lbs for the first 3 months
- ◆ **Pregnancy**
 - Delayed for at least 1 year
 - Ideally on tacrolimus

Promoting Health After Liver Transplant (2 of 3)

- ◆ **Follow national guidelines**
- ◆ **Bone density scan** to monitor for osteopenia/osteoporosis
 - Yearly for osteopenic patients, every 2-3 years with normal BMD
- ◆ **Dermatological examination** to screen for skin cancer
- ◆ **Dental Examination**
- ◆ **Female patients:** pap smear and mammogram
- ◆ **Colonoscopy**
- ◆ **Vaccinations** per the transplant Institute protocol
 - ⊘ No vaccines for the first 6 months post transplant
 - ⊘ No live vaccines
- ◆ **HCC surveillance**

Promoting Health After Liver Transplant (3 of 3)

- ◆ **Cardiovascular disease and renal failure are the leading non-hepatic causes of morbidity and mortality late after LT**
- ◆ **Renal**
 - Kidney dysfunction, may require dialysis or kidney transplant
- ◆ **Cardiovascular**
 - Diabetes, obesity, hypertension, & hyperlipidemia
 - Lifestyle changes (diet and exercise)
 - Medications as indicated
 - Routine follow-up with PCP

TABLE 2. PREVALENCE OF CARDIOVASCULAR RISK FACTORS AND CKD IN LT RECIPIENTS BEYOND THE FIRST POSTTRANSPLANT YEAR

	PREVALENCE RATE
Cardiovascular risk factor	
Metabolic syndrome*	50%–60%
Systemic hypertension	40%–85%
DM	10%–64%
Obesity	24%–64%
Dyslipidemia	40%–66%
Cigarette smoking	10%–40%
CKD (stage 3-4) [†]	30%–80%
End-stage kidney disease	5%–8%

*Any 3 of the following: hypertension, obesity, dyslipidemia, and DM.
†Estimated glomerular filtration rate. 15 to <60 mL/minute/1.73 m².

Complications

Liver Transplant

Abnormal Liver Tests

◆ Timing

1. Early: 0-1 month

- Infection (donor, technical, nosocomial)
- Primary nonfunction (PNF)
- Rejection
- Hepatic artery thrombosis (HAT)
- Bile leak
- Biliary stenosis

2. Intermediate: 1-6 months

- Infection/CMV (opportunistic)
- Rejection
- Biliary complications
- Recurrent disease

3. Late: >6 months

- Infection (community)
- Rejection
- Recurrent disease

Primary Nonfunction (PNF)

- ◆ Graft failure that occurs within 7 days of transplant
- ◆ Occurs between 2-10% of LT patients
- ◆ **Findings**
 - Elevated LFTs,
 - Elevated INR
 - Elevated ammonia
 - Poor bile production
 - **Patent** hepatic vessels
- ◆ **Donor risk factors:**
 - Advanced age
 - Steatosis
 - Stroke as cause of death
 - Prolonged ischemia time
- ◆ **Recipient risk factors**
 - Renal insufficiency
 - Retransplantation
- ◆ **Treatment**
 - Requires urgent retransplantation

Primary Nonfunction (PNF)

What happens after PNF/Retransplant?

- ◆ Data obtained from UNOS for all adults who received a deceased donor liver transplant between January 1990 and December 2004
- ◆ 2,061 of 58,576 (3.5% overall) met PNF criteria
- ◆ 1121 re-transplanted (54%), 940 died (46%)

Patient Survival After PNF – IF RETRANSPLANTED			
	1 yr survival	3 yr survival	5 yr survival
Primary Function	87%	79%	73%
PNF/Retxp	67%	61%	54%

Long-term Analysis of Primary Nonfunction in Liver Transplant Recipients

N. Kemmer, M. Secic, V. Zacharias, T. Kaiser, and G.W. Neff

Rejection



Up to 30% have at least one episode of rejection

Diagnosis: Liver biopsy is gold standard

Clinical Findings

- Usually asymptomatic
- Elevated liver numbers
- May have pre-transplant symptoms

Different kinds based on timing from transplant:

- **Hyperacute:** minutes to days post-LT; often irreversible and requires immediate re-transplant
- **Acute:** up to 3 months post-LT; reversible with high dose steroids or thymoglobulin
- **Chronic:** over longer time period, generally months; may lead to retransplant

Rejection: Acute

- ◆ Graft inflammation mediated by killer T cells that develop in response to donor antigens from the transplanted organ
- ◆ Majority occur within 3 months post-LT
- ◆ Most common and responsive form
- ◆ **Risk factors:**
 - Inadequate IS (most common)
 - Autoimmune liver disease
 - Female recipient of a male donor organ
- ◆ **Treatment:**
 - High dose corticosteroids
 - Adjust IS
 - increase dosages of current meds
 - add new agent
 - or switch medications
 - Thymoglobulin as last resort

Rejection: Chronic

- ◆ Occurs several months post-LT
- ◆ Worse prognosis than acute rejection
 - Results in graft failure with eventual loss
- ◆ Occurs in 3-4% of LT patients
- ◆ **Risk factors:**
 - Autoimmune liver disease
 - History of previous chronic rejection resulting in graft loss necessitating retransplant
 - CMV
 - African American
- ◆ **Treatment:**
 - Adjust IS
 - increase dose
 - add another agent

Case Study

- ◆ 20 y/o F, s/p OLT POD #12 for hepatitis B at MELD 30
- ◆ Explant: Chronic hepatitis
- ◆ Pre LT: ascites, encephalopathy, cholestasis with active viral hepatitis
- ◆ Post LT: tenofovir indefinitely, receive HBIG x 1 year
- ◆ Medications: tacrolimus 8 mg twice daily, and prednisone 20 mg daily, tenofovir, HBIG

	6/21 POD 8 (day of discharge)	6/25 POD 12
TACROLIMUS (FK506) ug/L	12.1	9.6
Bilirubin, Total 0.3 - 1.2 mg/dL	5.3 (A)	3.5 (A)
Bilirubin, Direct 0.1 - 0.5 mg/dL	3.2 (A)	1.7 (A)
Bilirubin, Unconjugated 0.2 - 0.7 mg/dL	2.1 (A)	1.8 (A)
ALT 14 - 54 U/L	91 (A)	496 (A)
AST 15 - 41 U/L	23	265 (A)
Alkaline Phosphatase 38 - 126 U/L	165 (A)	185 (A)
GAMMA GT 7 - 50 U/L	282 (A)	220 (A)

Case Study: Rejection

Index Discharge
Readmit
Discharge

↓
↓
↓

	6/21/2018 POD 8	6/25/2018 POD 12	6/27/2018 POD 14	6/28/2018 POD 15	7/3/2018 POD 20	10/2/2018 3mo 2 wk
TACROLIMUS (FK506) ug/L	12.1	9.6	10.2	12.3	12.5	7.1
Bilirubin, Total 0.3 - 1.2 mg/dL	5.3 (A)	3.5 (A)	2.7 (A)	2.4 (A)	1.9 (A)	0.7
Bilirubin, Direct 0.1 - 0.5 mg/dL	3.2 (A)	1.7 (A)	1.3 (A)	1.2 (A)		
Bilirubin, Unconjugated 0.2 - 0.7 mg/dL	2.1 (A)	1.8 (A)	1.4 (A)	1.2 (A)		
ALT 14 - 54 U/L	91 (A)	496 (A)	777 (A)	644 (A)	273 (A)	49
AST 15 - 41 U/L	23	265 (A)	236 (A)	125 (A)	60 (A)	21
Alkaline Phosphatase 38 - 126 U/L	165 (A)	185 (A)	161 (A)	150 (A)	100	70
GAMMA GT 7 - 50 U/L	282 (A)	220 (A)	191 (A)	174 (A)	109 (A)	37

- ◆ Diagnosis (biopsy): acute cellular rejection, mild
- ◆ Treatment: 1g solumedrol, 2 doses of 500mg solumedrol
- ◆ IS pre-rejection: tacrolimus 8 mg twice daily + prednisone 20 mg daily
- ◆ IS post-rejection: tacrolimus 12 mg twice daily + high dose prednisone taper + azathioprine 100 mg daily

Hepatic Artery Thrombosis (HAT)

- ◆ 2.6-6% in adults, 15-20% in pediatrics
- ◆ **Diagnosis:**
 - Doppler US: primary technique
 - Arteriography: gold standard but invasive
 - Usually <1 month after LT
- ◆ **Factors:**
 - No cause in many cases
 - Dissection of hepatic arterial wall
 - Previous transarterial chemoembolization (TACE)
 - Split and living related LT
 - Aberrant donor or recipient arterial anatomy
- ◆ **Clinical findings:**
 - Early → more aggressive, graft ischemia/necrosis, sepsis, increased transaminases
 - Late → biliary complications, may have preserved graft function
- ◆ **Treatment:**
 - Retransplant

Bile Leak

- ◆ Complicate 1-25% of LT and often occur within first few months
- ◆ Associated with decreased overall survival
- ◆ **Can occur at the following locations:**
 - Site of anastomosis
 - Within the liver due to bile duct destruction
 - Cut surface in a split liver or after a liver biopsy
- ◆ **Clinical Findings:**
 - Bile-stained fluid in JP drain
 - Peritonitis with systemic signs of sepsis
 - Elevated WBC and bilirubin levels
- ◆ **Treatment:**
 - Inserting stents via an endoscopic retrograde cholangiopancreatography (ERCP)
 - Percutaneous Transcholangiography (PTC) if Roux-en-Y
 - Surgery for those with large leaks or frequent stents to switch anastomosis from duct-to-duct to a roux-en-y

Biliary Stricture

- ◆ Complicate 3-14% of all liver transplants
- ◆ **Findings**
 - Elevated alk phos, GGT, and bilirubin
 - May remain undetected until infection appears
- ◆ **Diagnosis and treatment:**
 - ERCP:
 - duct-to-duct recipients
 - Stent may be placed to keep the bile duct open
 - Requires a follow up appointment in 1-3 months for another ERCP to either remove the stent, or reinsert another if the stricture is not corrected
 - PTC
 - May be attempted to repair the stricture and/or insert a stent.
 - Exploratory lap may be required due to the difficulty manipulating the bile ducts.
 - Surgery:
 - If require frequent ERCPs with stenting, may need Roux-en-Y to fix this chronic condition.

Infection: CMV

- ◆ **Most significant pathogen** affecting LT recipients
- ◆ All patients who are CMV- and receive CMV+ donor should receive prophylaxis with IV ganciclovir for at least 3 months post transplant
- ◆ **Risk factors for viremia:**
 - CMV+ donors into CMV- recipients
 - First 3 months post transplant
 - Rejection
 - Coinfection with other viruses, bacteria, or fungi
- ◆ **Symptoms:**
 - Bone marrow suppression
 - Diarrhea
 - Abdominal pain
- ◆ **Treatment:**
 - Reduce IS
 - High dose IV ganciclovir or PO valganciclovir if mild to moderate disease without GI involvement
 - Watch liver numbers closely, CMV may precipitate rejection episode

Liver: 1 Year Post-Transplant Outcomes

	Penn Outcomes	SRTR Expected	National Average
Graft (Organ) Survival	91.80%	91.01%	90.42%
Patient Survival	94.54%	92.86%	92.55%

July 2018 PSR: Transplants performed between 01/01/2015 and 06/30/2017

Source: <http://www.srtr.org/>

These outcomes meet Medicare requirements.

References

- ◆ Busuttil, R., Klintmalm, G. Transplantation of the Liver. Ed.3. Philadelphia, Pennsylvania: Elsevier Inc., 2015.
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