Post-Liver Transplant Follow-up
What To Do With Elevated Liver Enzymes?

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Disclosures

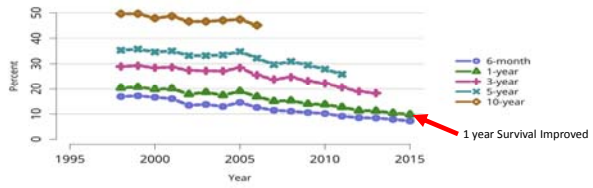
Speaker's Bureau
- Gilead Pharmaceuticals
- Abbvie Pharmaceuticals
- Merck Pharmaceuticals

Research
- Intercept Pharmaceuticals

Key Points

- Locally transplant survival at 1 year exceeds 90%
- Surgical complications predominate the first year
- Long-term complications largely arise from recurrent liver disease and immunosuppresants
- Evaluation of liver test abnormalities should be programmatic in all cases

Reason for Lecture: Survival Increasing



SRTR Database January 2018

Survival Increasing

as of January 2018

Deceased Donor

	UAB	Expected	National
1 Year Liver Survival	91%	91%	90%
1 Year Patient Survival	93%	93%	92%

One Year Cohort for Transplants Performed between 7/1/2014 and 12/31/2016

SRTR Database January 2018

Post-Liver Transplant Follow-up Complications

Early- First Year

Mostly "Surgical" Complications
- Rejection
- Vascular
- Biliary

Late- > 1 Year

Mostly "Medical" Complications
- Recurrent Liver Disease
- Infections
- Malignancy

Key Point

WHEN EVALUATING ELEVATED LAE'S AFTER TRANSPLANT START WITH "EARLY" COMPLICATIONS!!

Post-Liver Transplant Follow-up Early Complications-Rejection

- Most within first 90 days
- Around 15% of transplant recipients impacted
- Increased association with autoimmune liver diseases

Cheung et al. Clin Liver Dis 2017;21:789-813.

Early Complications-Rejection Diagnosis

Usually asymptomatic

Elevated liver enzymes seen

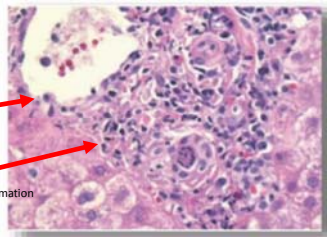
Liver biopsy mandated in virtually all cases

Levitsky, et al. Clin Gastroenterol Hepatol 2017;15:584-593.

Early Complications-Rejection Diagnosis

Biopsy Findings:

- "Endothelitis"
- Portal tract/Bile duct inflammation
  - Overlap with other primary liver disease
    - Autoimmune hepatitis
    - Viral Hepatitis
    - Drugs
    - Cholestatic liver disease



Not Always Classical!

Pereira, E. Transplant Pathology
Levitsky, et al. Clin Gastroenterol Hepatol 2017;15:584-593.

Early Complications-Rejection Treatment

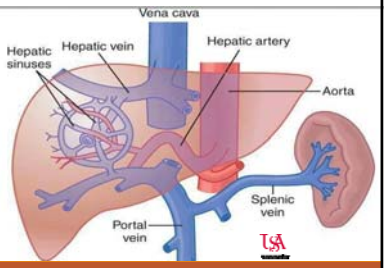
If found early a large proportion respond

- Initial
  - Methylprednisolone bolus
  - Oral steroid taper
- Maintenance
  - Increase level of immunosuppression

Cheung et al. Clin Liver Dis 2017;21:789-813.

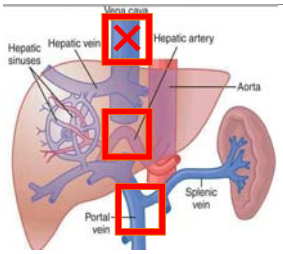
Post-Liver Transplant Follow-up Early Complications-Vascular

- Complications at anastomoses
  - Hepatic Artery
  - Portal Vein
  - Inferior Vena Cava



Cheung et al. Clin Liver Dis 2017;21:789-813.

Early Complications-Vascular

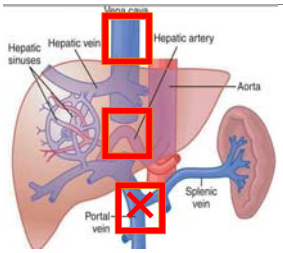


IVC Stenosis

- Uncommon
- Usually size mismatch
- Presentation
  - Graft dysfunction
  - Ascites
- Diagnosis
  - Ultrasound with dopplers
- Therapy
  - Endovascular stenting
  - Rarely Re-transplantation

Cheung et al. Clin Liver Dis 2017;21:789-813.

Early Complications-Vascular

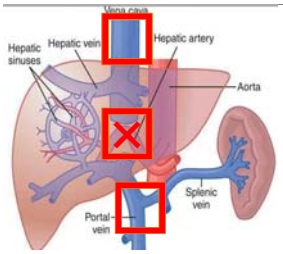


Portal Vein Thrombosis

- Presentation
  - NO Graft dysfunction
    - Usually Normal Liver Enzymes
  - Ascites/Variceal bleeding
- Diagnosis
  - Ultrasound with dopplers
- Therapy
  - Anticoagulation
  - Rarely Re-transplantation

Cheung et al. Clin Liver Dis 2017;21:789-813.

Early Complications-Vascular



Hepatic Artery Thrombosis

- Most severe
- Hepatic artery ONLY supply to bile ducts
- Presentation
  - Cholestatic elevations LAE's
  - Graft dysfunction
- Treatment
  - Bile duct
    - Endoluminal stenting
    - Surgical repair
  - Endovascular stenting to artery
  - May require re-transplantation

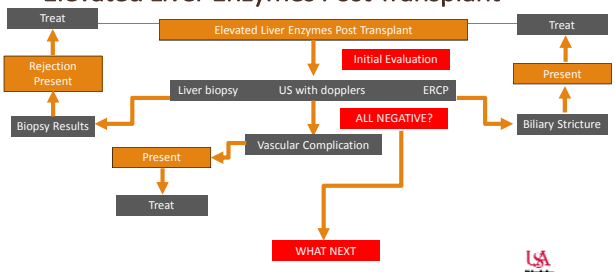
Cheung et al. Clin Liver Dis 2017;21:789-813.

Post-Liver Transplant Follow-up Early Complications-Biliary

- Most common post transplant complication
- Multiple causes
  - Anastamotic
    - Surgical technique
  - Non-anastamotic
    - CMV Infection
    - ABO incompatibility (RARE)
    - Prolonged cold ischemia time
- Treatment
  - Endoscopic stenting
  - Operative repair (i.e hepaticojejunostomy)

Cheung et al. Clin Liver Dis 2017;21:789-813.

Elevated Liver Enzymes Post Transplant



Key Point

WHEN EVALUATING ELEVATED LAE'S AFTER TRANSPLANT START WITH EARLY COMPLICATIONS!!

IF EVALUATION FOR REJECTION AND STRICTURES NEGATIVE, CONSIDER RECURRENT LIVER DISEASE

Post-Liver Tranpslant Follow-up Complications

Early- First Year

Mostly "Surgical" Complications
- Rejection
- Vascular
- Biliary

Late- > 1 Year

Mostly "Medical" Complications
- Recurrent Liver Disease
- Infections
- Malignancy

Post-Liver Transplant Follow-up Recurrent Liver Diseases

Don't Recur After Transplant
- Alpha-1-Antitrypsin Deficiency
- Hereditary Hemochromatosis
- Alcoholic Liver Disease
  - If Abstinent
  - Consider serum phosphatidylethanol screening

May Recur after Transplant
- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- Autoimmune Hepatitis
- NAFLD

Always Recur After Tranpslant
- Hepatitis B
- Hepatitis C

Post-Liver Transplant Follow-up Recurrent Liver Diseases

Always Recur After Tranpslant
- Hepatitis B
- Hepatitis C

- Hep B Sag + Recipient
  - Lifelong Antiviral Therapy
    - New potent nucleos(t)ide preferred
      - Entecavir (most data)
      - Tenofovir
    - Older therapies should be avoided (resistance)
      - Adefovir
      - Lamivudine
  - HBIg (controversial)
    - Should be used if high levels HBV DNA at Transplant
    - Data lacking if HBV DNA undetectable with newer agents

Given High Barrier to Resistance of New Therapies if Elevated HBV DNA, Consider Non-Compliance

Wang P. PLOS ONE 9(8): e104480.
Mukherjee S. J Antivir Antiretrovir 1: 017-027.

Post-Liver Transplant Follow-up Recurrent Liver Diseases

Always Recur After Tranpslant
- Hepatitis B
- Hepatitis C

- Hep B Sag (–) and Hep B Core Ab + Donor
  - IF + Hep B Sab (Native Immunity)
    - Consider q 3 months x 1 year then q 6months HBV DNA and Hep B Sag
  - If – Hep B Sab (No Native Immunity)
    - HBIg
      - Length of therapy is controversial
    - Antiviral therapy indicated

Mukherjee S. J Antivir Antiretrovir 1: 017-027.

Post-Liver Transplant Follow-up Recurrent Liver Diseases

Always Recur After Tranpslant
- Hepatitis B
- Hepatitis C

- Still leading cause of hepatic transplantation
- HCV viremia occurs within hours after transplantation if viremic at time of tranpslant
- New DAA therapy is effective in nearly all patients

With Effective Therapy When Should You Treat?

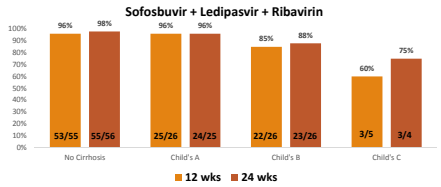
Cheung et al. Clin Liver Dis 2017;21:789-813.

Decompensated Liver Disease - Controversies

When is it too late to treat????
- How much liver function will recover?
- Are there certain complications less likely to reverse?
- Are patients going to remain in "transplant list purgatory" forever?
- Patients no longer eligible for HCV (+) organs

Should we allow patients to be transplanted, then treat?

Post Liver Transplantation



Current regimens work after transplant!!

Charlton M, et al. Gastroenterology 2015;149:649-659

When is it too late?

- There is no currently accepted strategy
- Some data to suggest increase death/ADR:
  - MELD >18
  - CTP-B/C
- Strongly consider evaluation prior to treatment:
  - MELD >15
  - Portal hypertensive related complications even with MELD <15
    - Ascites
    - Varices
    - Overt Hepatic Encephalopathy
- Risk/Benefit discussion important

Fernandez-Carrillo et al EASL Abstract GS01

Immediately Post Liver Transplant: Recommended Regimens

Genotype 1, 4, 5, 6
- Sofosbuvir + Ledipasvir+ Ribavirin 600mg- 12 weeks*
- Glecaprevir + Pibrentasvir -8 weeks

Genotype 2, 3
- Sofosbuvir + daclatasvir + Riba 600mg -12 weeks
- Glecaprevir + Pibrentasvir -8 weeks

NOT ALL REGIMENS APPROVED AFTER TRANSPLANT

*Data exists for use without ribavirin

Difficult to Keep It All Straight!

AASLD/ISDA Guidelines
http://hcvguidelines.org

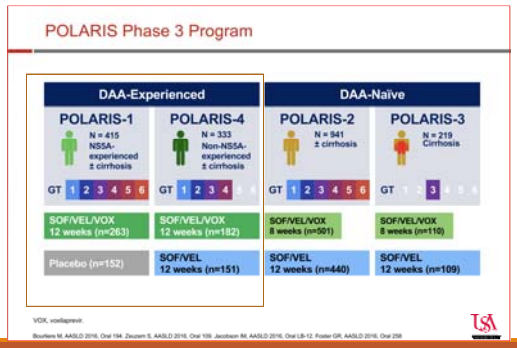
- Continuously updated
- Sets the standard of care for HCV in the US
- May be useful in obtaining insurance approval

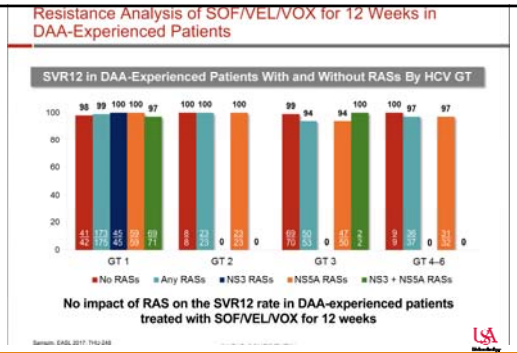
Immediately Post Liver Transplant: Recommended Regimens

Very few interactions with standard immunosuppresion

- Sofosbuvir + Ledipasvir
  - No dose adjustment with tacrolimus
  - No dose adjustment with cyclosporine
- Glecaprevir + Pibrentasvir (GP)
  - Protease inhibitor can boost immunosuppresion levels
    - Tacrolimus
      - No adjustment follow levels/ toxicity
    - Cyclosporine
      - **DO NOT** GP use this if >100mg dose of cyclosporine

What about treatment failures?





What about treatment failures?

Currently not enough data for recommendations

Sofosbuvir, velpatasvir, voxilaprevir

- Tacrolimus
  - No Dose adjustment needed
- Cyclosporine
  - Voxileprevir significantly boosts levels not recommended

Must take each case individually

Key Point

IN PATIENTS WITH ACTIVE HCV, EVEN IF LOW MELD CONSIDER TRANPSLANT EVALUATION IF DECOMPENSATING FEATURES

Post-Liver Transplant Follow-up Recurrent Liver Diseases

May Recur after Transplant

- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- Autoimmune Hepatitis
- NAFLD

Recurrent Liver Diseases : Primary Biliary Cholangitis

Recurrence reported up to 14-45% at 15 years

Difference due to different diagnostic criteria

Graft loss is rare

- Less than 2%

Edmunds Transplantation 2016;100: 515–524
Intractable Rare Dis Res. 2012 May; 1: 66–80

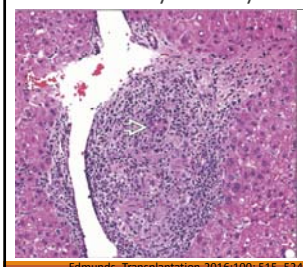
Recurrent Liver Diseases : Primary Biliary Cholangitis

Diagnosis:

- Symptoms of pruritis and fatigue usually absent
- Alkaline phosphatase typically NOT elevated
- Anti-mitochondrial antibodies unreliable
- Tissue diagnosis is necessitated

Edmunds Transplantation 2016;100: 515–524
Intractable Rare Dis Res. 2012 May; 1: 66–80

Recurrent Liver Diseases : Primary Biliary Cholangitis



Biopsy Findings:

Diagnostic criteria for recurrent PBC

Liver transplant for well-described PBC

AMA seropositive after liver transplant

Liver histology with the following characteristics

- Mononuclear inflammatory infiltrate
- Lymphoid aggregates
- Epithelioid granuloma formation
- Bile duct destruction

Definite recurrent PBC:

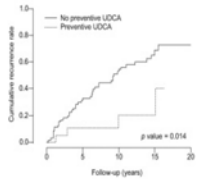
- 3 of 4 portal tract lesions are observed

Probable recurrent PBC:

- 2 of 4 portal tract lesions are observed

Edmunds. Transplantation 2016;100: 515–524
Intractable Rare Dis Res. 2012 May; 1: 66–80

Recurrent Liver Diseases : Primary Biliary Cholangitis



Prevention

- UCDA shown to decrease risk of recurrence
- Well tolerated
- At current no long term survival benefit

Treatment

- Studies have shown UCDA normalized enzymes
  - UCDA- 52%
  - Placebo- 22%
- No significant changes in histologic progression

Edmunds Transplantation 2016;100: 515–524
Intractable Rare Dis Res. 2012 May; 1: 66–80
Bosch A. J Hepatol. 2015;63:1449-58

Post-Liver Transplant Follow-up
Recurrent Liver Diseases

May Recur after Transplant

- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- Autoimmune Hepatitis
- NAFLD

Recurrent Liver Diseases :
Primary Sclerosing Cholangitis

Recurrence reported from 10-37%

Diagnosis is difficult

- Multiple other diagnosis can resemble

Graft loss can be significant

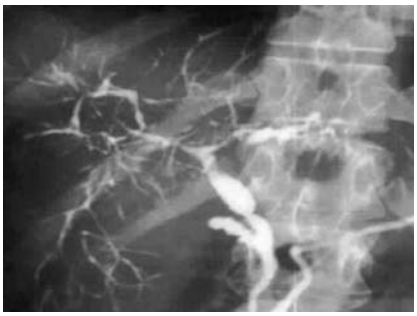
Edmunds Transplantation 2016;100: 515–524
Cheung et al. Clin Liver Dis 2017;21:789-813.

Recurrent Liver Diseases :
Primary Sclerosing Cholangitis

Diagnosis:

- Considered when elevated liver enzymes seen
- Imaging is required
- NO serologic test is convincing
- Even after transplant remains a diagnosis of exclusion

Edmunds Transplantation 2016;100: 515–524
Cheung et al. Clin Liver Dis 2017;21:789-813.

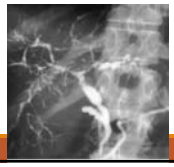


Scenario:

28 year old male transplanted for PSC 2 years prior
- History of HIV (C3) prior to transplant (CD4 250 prior to transplant)

- What is the diagnosis?
  - Recurrent PSC?
  - Hepatic artery thrombosis?
  - Chronic isospora infection?

ON IMAGING IS THE SAME!!



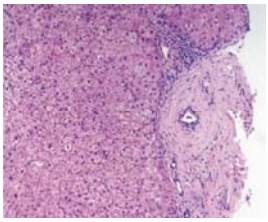
Recurrent Liver Diseases : Primary Sclerosing Cholangitis

Diagnosis:
- DIFFICULT!
  - Criteria
    1. Known PSC prior to transplant
    2. Cholangiogram with intra/extrahepatic bile duct dilation with beading
    3. Liver biopsy showing fibrous changes to bile duct AND:
       - A. No evidence of hepatic artery thrombosis
       - B. No known ABO Incompatibility
       - C. No ductopenic rejection (chronic)
       - D. No anastamotic strictures 90 days after transplant

REMAINS A DIAGNOSIS OF EXCLUSION!!

Liver Transplant 2009;15:S25-S39

Recurrent Liver Diseases : Primary Sclerosing Cholangitis



Prevention
- None known to prevent recurrence
- Lifelong steroids are used

Treatment
- UCDA not recommended

Liver Transplant 2009;15:S25-S39

Recurrent Liver Diseases : Cholestatic Liver Diseases

Special Considerations:

Even after transplant baseline risks remain:

- PBC and PSC
  - Aggressive screening for bone mineral health
  - Fat soluble vitamin screening
- PSC
  - If history of IBD
    - Annual colonoscopy for dysplasia screening

Lindor KT et al. Am J Gastroenterol.

Post-Liver Transplant Follow-up Recurrent Liver Diseases

May Recur after Transplant
- Primary Biliary Cholangitis
- Primary Sclerosing Cholangitis
- Autoimmune Hepatitis
- NAFLD

Recurrent Liver Diseases : Autoimmune Hepatitis

Recurrence reported up to 17-33%

Risk Factors
- Genetic Predisposition
- High grade inflammation in native liver
- Suboptimal immunosuppresion

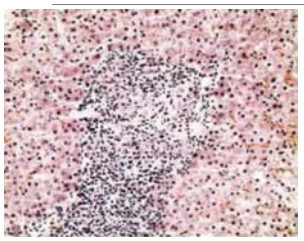
Liver Transplant 2009;15:S25-S39

Recurrent Liver Diseases : Autoimmune Hepatitis

Diagnosis:
- Elevated liver enzymes
- Auto-antibodies may or may not be helpful
  - If antibodies are elevated higher that pre-transplant can predict relapse
- Tissue diagnosis is necessitated

Liver Transplant 2009;15:S25-S39

Recurrent Liver Diseases : Autoimmune Hepatitis



Biopsy Findings:

Diagnostic criteria for recurrent AIH

- Transplantation for confirmed diagnosis of AIH
- Elevated transaminases
- Hyper-gammaglobulinemia (elevation of IgG)
- Presence of autoantibodies (ANA, SMA and/or Anti-LKM1)
- Compatible histopathology
  - Interface hepatitis,
  - Portal inflammation and/or lymphoplasmacytic infiltrates
- Response to corticosteroids
- Exclusion of differential diagnostic considerations

Edmunds. Transplantation 2016;100: 515–524

Recurrent Liver Diseases : Autoimmune Hepatitis

Prevention

- Lifelong dual immunosuppresion
- Lifelong steroids is controversial but widely accepted

Treatment

- Steroid bolus and taper
- Optimization of immunosuppresion

Transplant Direct. 2017;3:178
Liver Transplant 2009;15:S25-S39

Key Points

- Locally transplant survival at 1 year exceeds 90%
- Surgical complications predominate the first year
- Long-term complications largely arise from recurrent liver disease and immunosuppresants
- Evaluation of liver test abnormalities should be programmatic in all cases