Post-Liver-Transplant Complications Medical Disorders

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Post-Transplant Complications

- ***Time***
  - *Early: 0-1 month*
  - *Intermediate: 1-6 months*
  - *Late: > 6 months*
- ***Type***
  - *Infection*
  - *Allograft dysfunction*
  - *Biliary tract dz.*
  - *Disease recurrence*

Post Liver Transplant Complications: Early: 0-1 Month

- ***Infections***:
  - **Bacterial**; related to procedure →
    - pneumonia; - biliary sepsis;
    - wound infection; - catheter related,
    - c. difficile PMC
  - **Viral**:
    - HSV stomatitis, - HCV,
    - Hepatitis B (if without prophylaxis)
  - **Fungal**:
    - Candida, - Aspergillus
  - **Parasites**:
    - Strongyloides

Post Liver Transplant Complications: Early: 0-1 Month

- ***Allograft dysfunction***:
  - PNF in first two weeks
  - Acute cellular rejection
  - Small-for-size Syndrome
- ***Biliary tract***:
  - Bile leaks
  - Anastomosis disruption
  - Hepatic duct stricture/hepatic artery thrombosis
- ***Disease recurrence***: unusual

Post Liver Transplant Complications: Intermediate: 1-6 Months

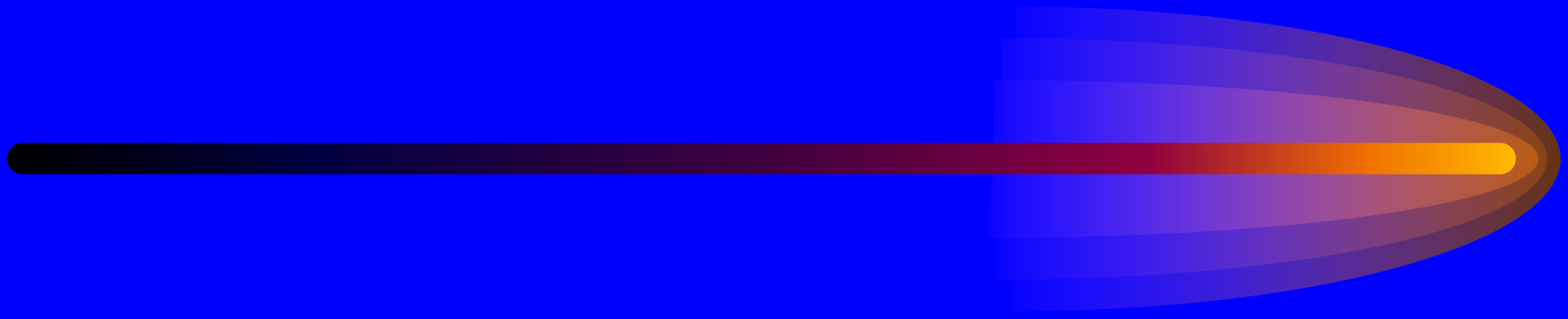
- ***Infections***:
  - **Viral**:
    - HHV6, - Adenovirus,
    - RSV, - Viral reactivation (CMV, EBV,VZV,HCV,HBV),
  - **Bacterial**:
    - Listeria, - Nocardia,
    - TB,
  - **Fungal**:
    - Pneumocystis, - Aspergillus,
    - Cryptococcus, - Hystoplasma,
    - Coccidioides,
  - **Parasites**:
    - Toxoplasma, - Strongyloides,
    - Leishmania, - Trypanosoma

Post Liver Transplant Complications: Intermediate: 1-6 Months

- ***Allograft dysfunction***:
  - Recurrent HCV
  - Rejection
  - Hepatic artery thrombosis
- ***Biliary tract***:
  - Biliary stricture
  - Leak associated with T-tube removal
- ***Disease recurrence***:
  - HCV,
  - PBC,
  - PSC (if after > 90 days),
  - Alcohol (rarely)

Post Liver Transplant Complications: Late: > 6 Months

- ***Infections***:
  - Community acquired infections (UTI, pneumonia)
  - VZV, CMV, influenza, papillomavirus, PTLD
- ***Allograft dysfunction***:
  - Chronic Rejection
  - Lymphoproliferative Syndrome (PTLD)
  - Underlying Disease
- ***Biliary tract***: < 4% per year
- ***Disease recurrence***: HCV, PBC, PSC, alcoholism within two years



Allograft Dysfunction

Graft Complications 0-1 month

- **<u>Primary Nonfunction</u>**:
  - Occurs in 4-10% LTX.
  - **Features**: hepatic encephalopathy, coagulopathy, minimal bile output, renal & multisystem failure, persistent hypothermia, hemodynamic instability, high lactate & liver enzymes, and hepatocyte necrosis, ***without*** vascular complication.
  - Those with hemodynamic instability or multiorgan failure need urgent retransplantation.

Criteria for 1A Status

Primary Non-Function

- Non function in first 7 days, and:
- AST > 3000 IU and at least one:
  - INR >/= 2.5
  - Arterial pH </= 7.3 or Venous pH </= 7.25, and/or Lactate >/= 4 mMol/L
- Anhepathic Phase

- No AST requirement for recipient of segmental grafts of LDLT

Allograft Complications 0-1 month

- **Primary Nonfunction**:
  - **Donor risk factors**:
    - **prolonged cold ischemia,**
    - **unstable donor,**
    - **high steatosis,**
    - **older age,**
    - **hypernatremia,**
    - **non-heartbeating**

Allograft Complications 0-1 month
"Small-for-Size" Syndrome

- Partial liver graft unable to meet functional demands of recipient: poor early graft function in absence of ischemia.
- Prevention: in cirrhotic GWBWR must be =/> 0.85%
- Manifestations:
  - Poor bile production
  - Prolonged cholestasis
  - Significant ascites
  - Coagulopathy

Allograft Complications 0-1 month
"Small-for-Size" Syndrome

- Biochemical profile:
  - Elevated Direct (& total) bili
  - Mild/moderate elevation of ALT & AST
  - Prolonged PT
- Histologic Features:
  - Cholestasis with "bile plugs"
  - Areas of regeneration & ischemia with patchy necrosis.
- Prognosis: 50% of recipients will die of sepsis within 4-6 weeks.

Allograft Complications at any time
Acute Allograft Rejection

- **Features**:
  - Portal infiltrate with mixed inflammatory cells
  - Bile duct injury
  - Endothelialitis
- **Grades (Banff Criteria)**
  - **I (mild):** cellular infiltrate in < 50% triads, mild, and within portal spaces.
  - **II (moderate):** cellular infiltrate in > 50% triads
  - **III (severe):** as in moderate + spillover into periportal areas + moderate/severe perivenular inflammation with perivenular-hepatocyte necrosis.

Allograft Complications at any time
PTLD

- **<u>Post-Transplant Lymphoproliferative Disorder</u>**

  T-lymphocytes are supposed to regulate B-cell proliferation due to EBV; In PTLD immunosupression affects T-cell immunity allowing unregulated proliferation.

  - **B-cell proliferation in nodal & extranodal sites; may involve transplanted organ.**
  - **Median time: 10 mo post-LTx.**
  - **Child/adult=3/1.**
  - **Survival: 1-y = 85%; 20-y = 45%.**
  - **Better survival if:**
    - **limited dz,** **- polymorphic/polyclonal dz,**
    - **in children,** **- on tacrolimus.**

Allograft Complications at any time
PTLD

- **…PTLD**

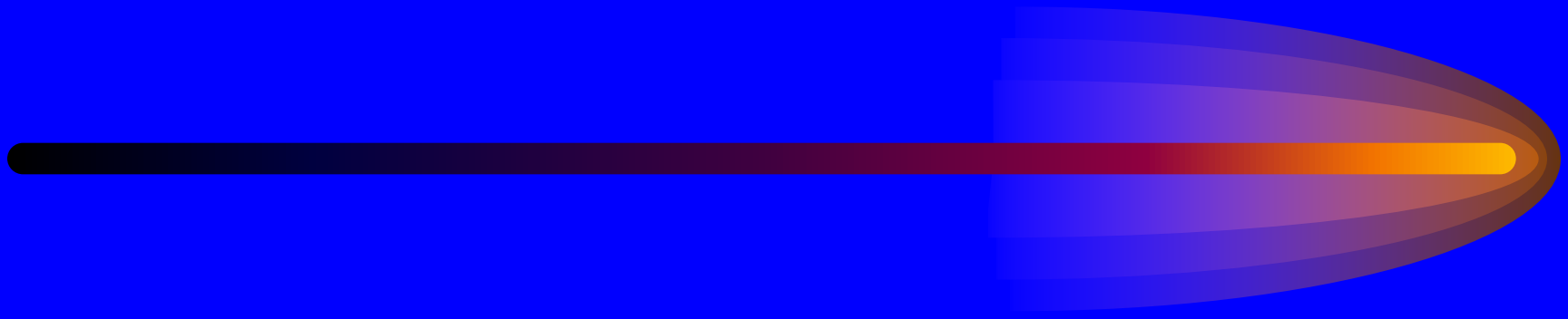
  DX: Bx with hyperplastic or neoplastic growth of B-cells which are receptor CD20(+) .

  – **Risk factors:**
    - **pre-LTx EBV sero-negativity,**
    - **steroid bolus,**
    - **CMV disease,**
    - **blood products.**
    - **excessive immunosupression (OKT3, ATGAM, Thymoglobulin),**

Allograft Complications at any time

PTLD

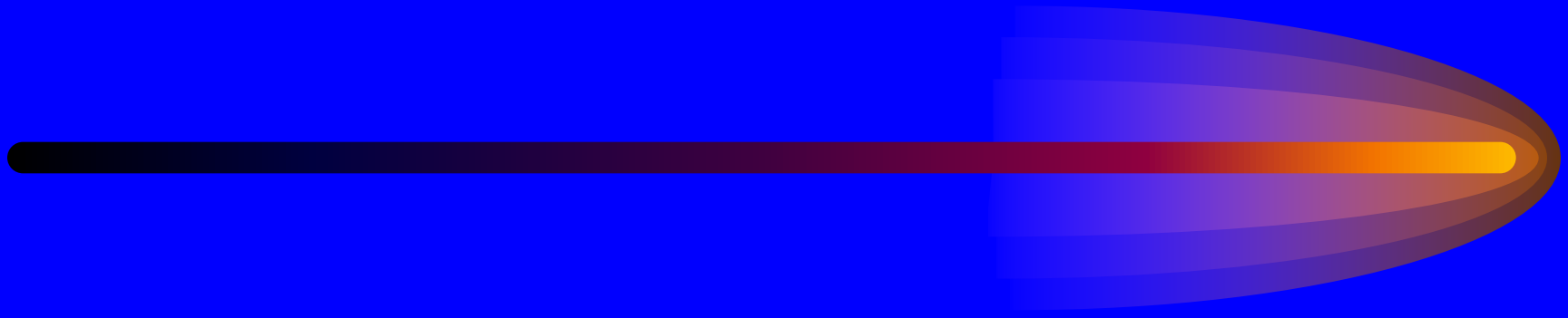
- **THERAPY OF PTLD**
- **Limited Disease (one site only)**
  - Surgical extirpation or localized radiation
  - Minor/moderate immunosuppression reduction (25%)
- **Extensive disease (more than 1 site)**
  - Intense immunosuppression reduction (50%)
  - Extirpation of local disease.
  - Rituximab
  - Chemotherapy (CHOP), for Rituximab failure or poor prognosis
  - In CNS involvement, radiation without chemotherapy.
- **Critically ill**
  - **Stop all immunosuppression except Prednisone**



Infections

Post Liver Transplant Complications: Infections

- More than 2/3 patients will develop infections in the 1st year.
- Infections are the leading cause of death.
- Complication of overimmunosuppression
- **Risk increased by**:
  - acute rejection,
  - re-transplantation,
  - HIV,
  - hepatitis B or C.



Bacterial Infections

Post Liver Transplant Complications: Bacterial Infections

- More common in 1st two months & most frequently located in the abdomen.
- **General Risk factors**:
  - rejection, - s/p acute liver failure,
  - high bilirubin, - prolonged hospitalization,
  - long OR time, - long ICU stay.

Post Liver Transplant Complications: Bacterial Infections

- **<u>Bacteremia</u>**:
  - Most common pathogens:
    - S. aureus
    - Enterococcus.
  - Risk factors:
    - DM, - IV catheter,
    - CMV, - low albumin,
    - roux-en-y, - biliary stricture.

Post Liver Transplant Complications: Bacterial Infections

- **<u>Intra-abdominal & wound infections</u>**
  - ***do not decrease patient nor graft survival.***
  - **Risk factors**:
    - bile anastomotic leak, - high pre-op WBC,
    - long OR time, - ascites,
    - severe obesity, - low albumin,
    - high transfusion need, - OKT3 use.

Post Liver Transplant Complications: Bacterial Infections

- **Pneumonia**:
  - Bacteria & aspergillus in 1st month.
  - Legionella may be the cause early post-OLTx or post rejection therapy.
  - Splenectomy increases risk of opportunistic infection.
  - BAL & Bx are helpful.
- **Hepatic Artery Thrombosis (HAT)**

  occur in 7%; associated with:
  - bacteremia, - cholangitis,
  - liver abscess, - graft loss.

Post Liver Transplant Complications: Bacterial Infections

- **Legionella**:
  - Usually early post-OLTx or after rejection therapy
  - Fever, chills, malaise, dyspnea, non-productive cough, diarrhea.
  - CXR: unilateral or bilateral dense lung infiltrate.
  - **DX**: Legionella Ag in urine, fluorescent Ab in respiratory secretion
  - **Treatment**: fluoroquinolone or erythromycin

Post Liver Transplant Complications: Bacterial Infections

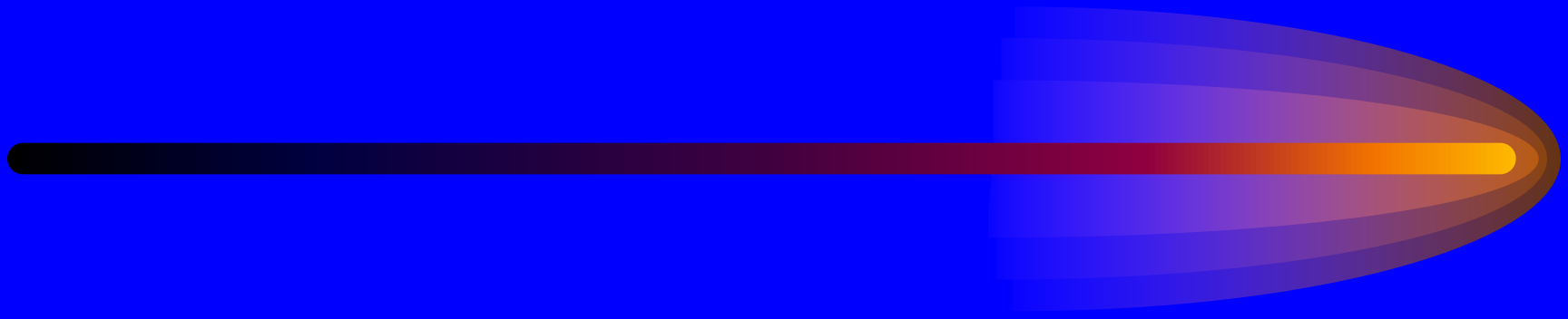
- **<u>Nocardia</u>**:
  - 0.7-3% of patients. N. asteroides is most common.
  - From 2nd month until years later.
  - May give: pneumonia, pulmonary nodules, lung abscess, brain abscess, meningitis, or skin lesions.
  - ***All patients should have brain imaging to R/O abscess.***
  - **DX**: branching gram(+) bacteria; positive culture.
  - **Treatment**: Bactrim or Minocycline.

Post Liver Transplant Complications: Bacterial Infections

- **Listeria monocytogenes**:
  - Usually from weeks to initial 2 months; infrequently years later.
  - Acquired from contaminated food.
  - May give: meningitis, meningo-encephalitis, encephalitis, bacteremia.
  - Rarely: pneumonia, arthritis, endophthalmitis, endocarditis, peritonitis, myocarditis, or hepatitis.
  - **Presentation**: fever, headache, meningismus, altered mentation, focal CNS findings, or seizures.
  - **DX**: Listeria in CSF or blood culture.
  - **Treatment**: Amp + Gent, or Bactrim

Post Liver Transplant Complications: Mycobacterial Infections

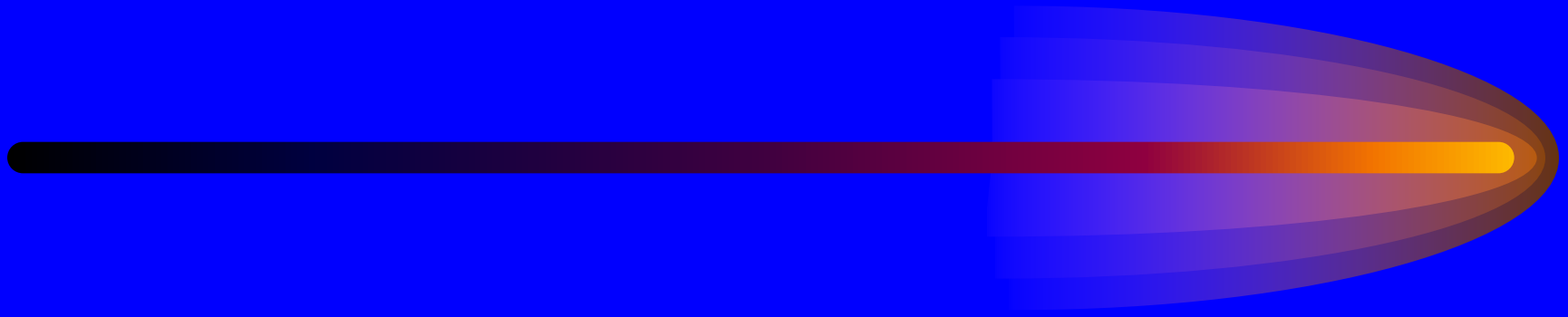
- **Tuberculosis**: Incidence is 1-6% in developed countries; high morbidity & mortality (up to 40%).
  - Mean onset is 9 months (15 days to years).
  - 50-66% have pulmonary TB.
  - Usually is reactivation of “dormant TB”.
  - Symptoms: fever, night sweats, weight loss.
  - **Pulmonary**: cough, dyspnea, pleuritic pain; may be miliary, focal or nodular; cavitary in 4%.
  - **Extrapulmonary**: gastrointestinal (ileitis, colitis, hepatitis, peritonitis; may cause GI bleed), genitourinary, skin, muscles, bones, lymph nodes, CNS.
- **Other Mycobacteria**: unusual in liver transplant. Most commonly pulmonary, pleural, or cutaneous.



Parasitic Infections

Post Liver Transplant Complications: Protozoal Infections

- **Toxoplasma gondii**:
  - uncommon except in heart Tx with allograft from infected donor.
  - TMP/SMX has decreased the risk.
  - May cause pneumonia as reactivated disease.
  - Diagnosis by BAL with direct immunofluorescence or PCR.
- **Others:**
  - **Strongyloides** (autoinfestation)
  - Giardia, Cryptosporidium, Isospora, Cyclospora, Microspora
  - Nematodes, Leishmania, Trypanosoma.



Fungal Infections

Post Liver Transplant Complications: Fungal Infections

- **Risk factors:**
  invasive infection likely with two of the following factors:
  - **creat > 3 mg/dL,**
  - **re-transplantation,**
  - **fungal colonization**
  - **OR time > 11 hours,**
  - **need for transfusion,**

  Other factors: CMV, HHV-6, HCV

Post Liver Transplant Complications: Fungal Infections

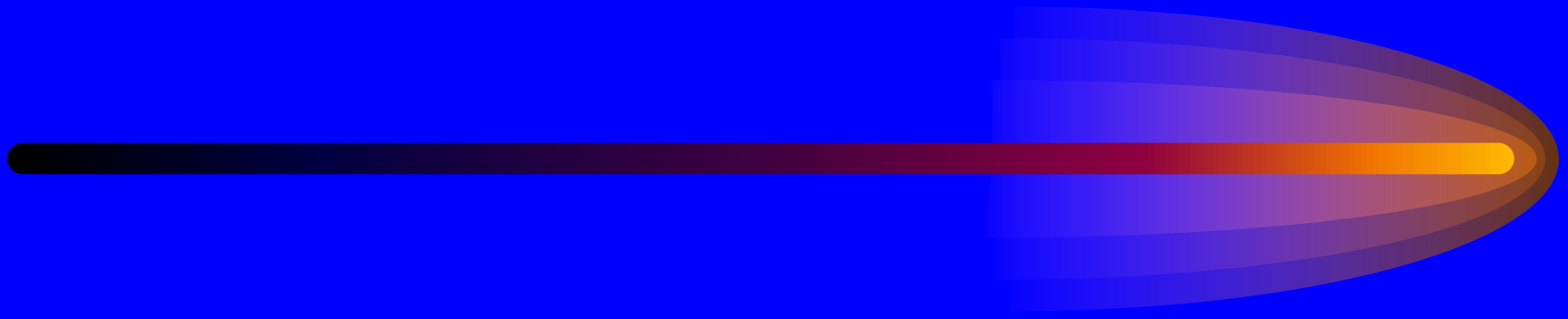
- **Candida**: most common fungal infection.
  - Risk factors: SBP prophylaxis, post-Tx dialysis, re-Tx.
- **Aspergillus**:
  - Second most common fungal infection.
  - High mortality (90%).
  - Median time: 17 d post-LTx.
  - Causes angioinvasion with tissue necrosis.
  - Aspergillus in sputum in Tx patient is probably invasive infection.

Post Liver Transplant Complications: Fungal Infections

- **Cryptococcus**:
  - most common cause of post-Tx meningitis.
  - Incidence=12/1000.
  - Mean time 30 mo post-LTx (1-146 mo).
  - May cause pneumonia (46%), meningitis (36%), other organ (11%), multiorgan (11%).
  - Mortality: 25%.
  - Infection may be subacute.
  - Cryptococcal serum Ag is good in meningitis, but only 40% (+) in pneumonia.

Post Liver Transplant Complications: Fungal Infections

- **<u>Pneumocystis jiroveci</u>:**
  - now very rare b/o TMP/SMX prophylaxis (5-10% of LTx in the past).
  - Most common 1-6 mo post Tx (up to 1 y).
  - Indolent fever, dyspnea, dry cough & hypoxemia.
  - CXR: Bilateral lung infiltrates.
  - BAL with immunofluorescence.
  - **Treatment**: TMP/SMX; if intolerant, aerosolized pentamidine.



Viral Infections

Post Liver Transplant Complications: Viral Infections

- **Cytomegalovirus**:
- Is immunomodulator virus; it is associated with fungal infections and chronic rejection.
  - CMV syndrome with fever, leukopenia & thrombocytopenia.
  - Pneumonia with diffuse infiltrates. Hepatitis. Retinitis.
  - Diagnosis by Bx findings, ophtalmoscopic exam, pp65 antigenemia, and/or quant PCR.
  - Risk factors: D+/R-, D+/R+, OKT3, Thymoglobulin, ATGAM.
  - **Treatment**: Ganciclovir IV or Valganciclovir po.
  - **Prophylaxis**: ganciclovir 1 gm TID po x 3 mo decreased CMV disease from 48.9% to 4.8%.
    Preemptive therapy is a reasonable alternative.

Post Liver Transplant Complications: Viral Infections

- **Epstein-Barr Virus**:
  - Signs & symptoms similar to CMV (fever, leukopenia, thrombocytopenia & atypical lymphocytosis in 50%; atypical presentation in 50%).
  - Reactivation most common in adults (90% sero-positive) & primary infection most common in children.
  - Most PTLD are due to EBV.

Post Liver Transplant Complications: Viral Infections

- **HSV & VZV:**
  - Pre-prophylaxis 1/3 patients had HSV disease.
  - Now HSV & VZV are rare b/o acyclovir or famciclovir use.
  - Hepatitis & pneumonitis may occur without skin lesions.
  - VZV vaccine can be given **before** Tx.
  - Post contact prophylaxis with VZV immunoglobulin is useful.

Post Liver Transplant Complications: Viral Infections

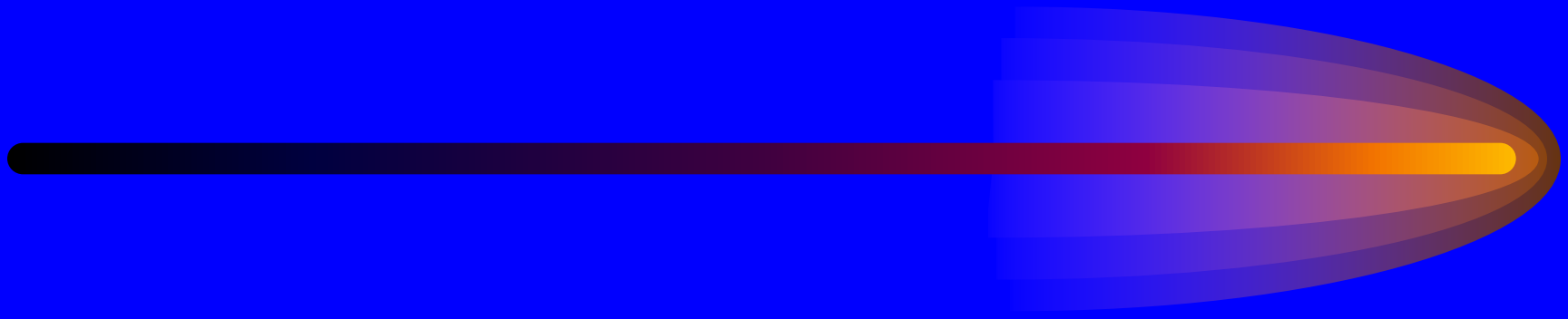
- **<u>Adenovirus</u>:**
  - More common in children.
  - May cause colitis, hepatitis, pneumonitis, hemorrhagic cystitis, encephalitis. ALF may occur.
  - Mimics CMV with fever, leukopenia, intranuclear inclusion bodies, and negative bacterial cultures.
  - Asymptomatic infection in 8-10% pediatric liver recipients.
  - Cidofovir or ribavirin may help.

Post Liver Transplant Complications: Viral Infections

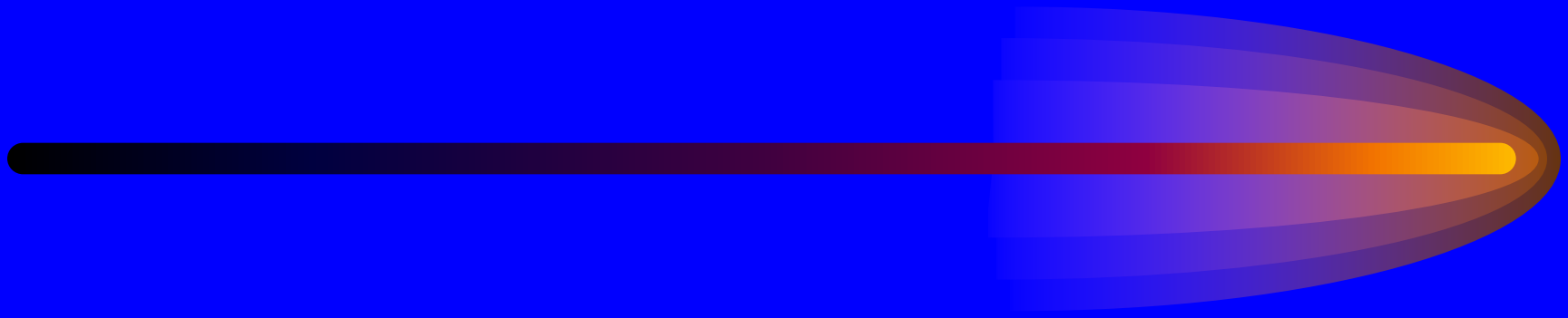
- **Human Herpesvirus 6:** is an immunomodulator virus and the agent of Roseola Infantum.
  - Most children sero-positive by age 2.
  - Reactivates wk 2-8 post-LTx.
  - Incidence: 14-82%.
  - **Symptoms**: fever, rash, pneumonitis, hepatitis, encephalitis.
  - Increases risk of invasive fungal infections.
  - **DX**: shell vial culture. Serology is not reliable. Antigenemia may be helpful. Serum PCR is too sensitive (overdiagnosis).
  - **Treatment**: ganciclovir, foscarnet, cidofovir.

Post Liver Transplant Complications: Viral Infections

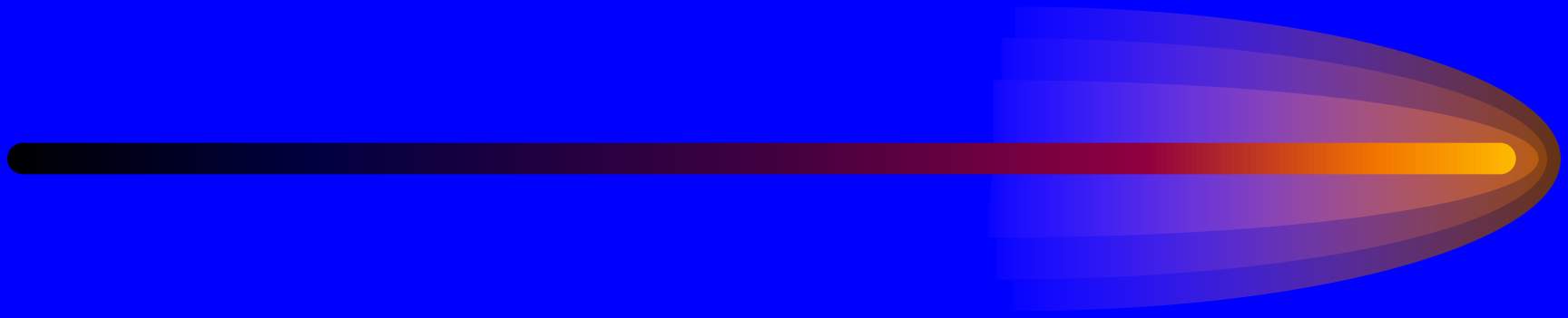
- **Human Herpesvirus 8**: causes Kaposi sarcoma, Castleman dz, and Primary Effusion Lymphoma.
  - Very rare; occurs in Liver Tx on CSA or Tacrolimus;
  - KS lesion in skin, viscera/liver.
  - Overimmunosupression increases risk.
  - **Treatment**: d/c or decrease immunosupression; bleomycin, doxorubicin, vincristine may help. Unknown if antivirals help.



Recurrent Disease



HBV prevention Post-OLTx



HBsAg(+) Recipient

Benefits of HBIG Prophylaxis

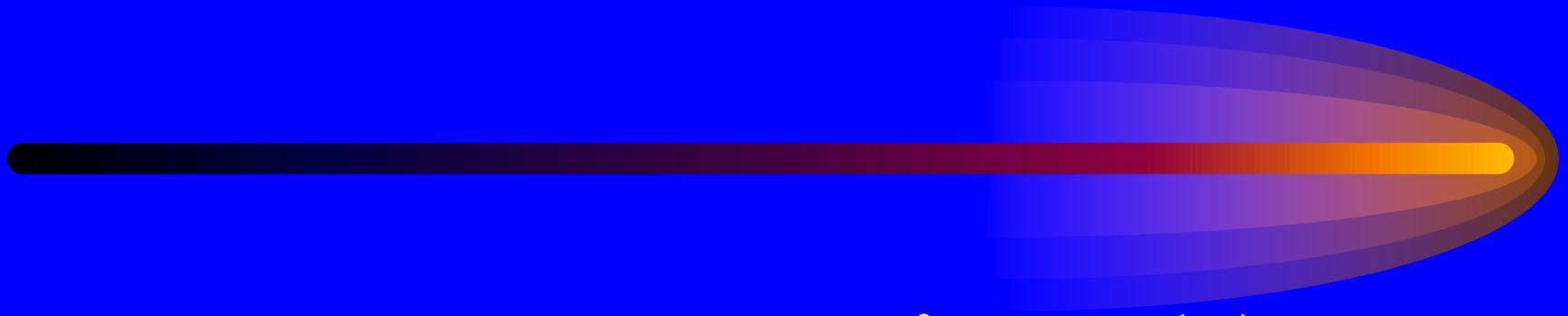
HBsAg(+) Recipient with Detectable HBV-DNA

- Without Prophylaxis: 5 year survival 40-60%
- With Prophylaxis survival is: 1 y = 91%, 5 y = 81%, 10 y = 73%
- Anti-HBs titer goals post-OLTx (in HBIG monotherapy):
  - a) first week: >500 IU/L,
  - b) week 2-4: >500 IU/L in high-replic; >100-150 in low-replic
  - c) day 28-180: >250 IU/L in high-replic; >100-150 in low-replic
  - d) thereafter: > 100-150 IU/L
- Escape occurs b/o:
  - a) “inadequate anti-HBs titer”, or
  - b) “pre-S/S mutation” causing reduced binding of anti-HBs.

HBsAg (+) Liver Transplant Recipient Prophylaxis

Recipient's Status	Anhepatic Phase	First week	Thereafter	Monitoring
HBV-DNA DETECTABLE, or HBV drug Resistance, or HIV, or HDV, or HCC, or Fulminant HBV (?)	HBIG 10000 IU, IV	HBIG 10000 IU, qd IV, x 6 days Entecavir, or Tenofovir, **for life**	HBIG 936 IU (3 mL Nabi-HB), IM on day 7, and q month for life Entecavir, or Tenofovir **for life**	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
HBV-DNA UNDETECTABLE without other risk factors.	No HBIG	Entecavir, or Tenofovir, **for life**	Entecavir, or Tenofovir **for life**	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life

Once HBsAg or HBV-DNA are (+), discontinue HBIG



Anti-HBc(+) organ
given to HBsAg(-) Recipients

Anti-HBc(+) organ donors

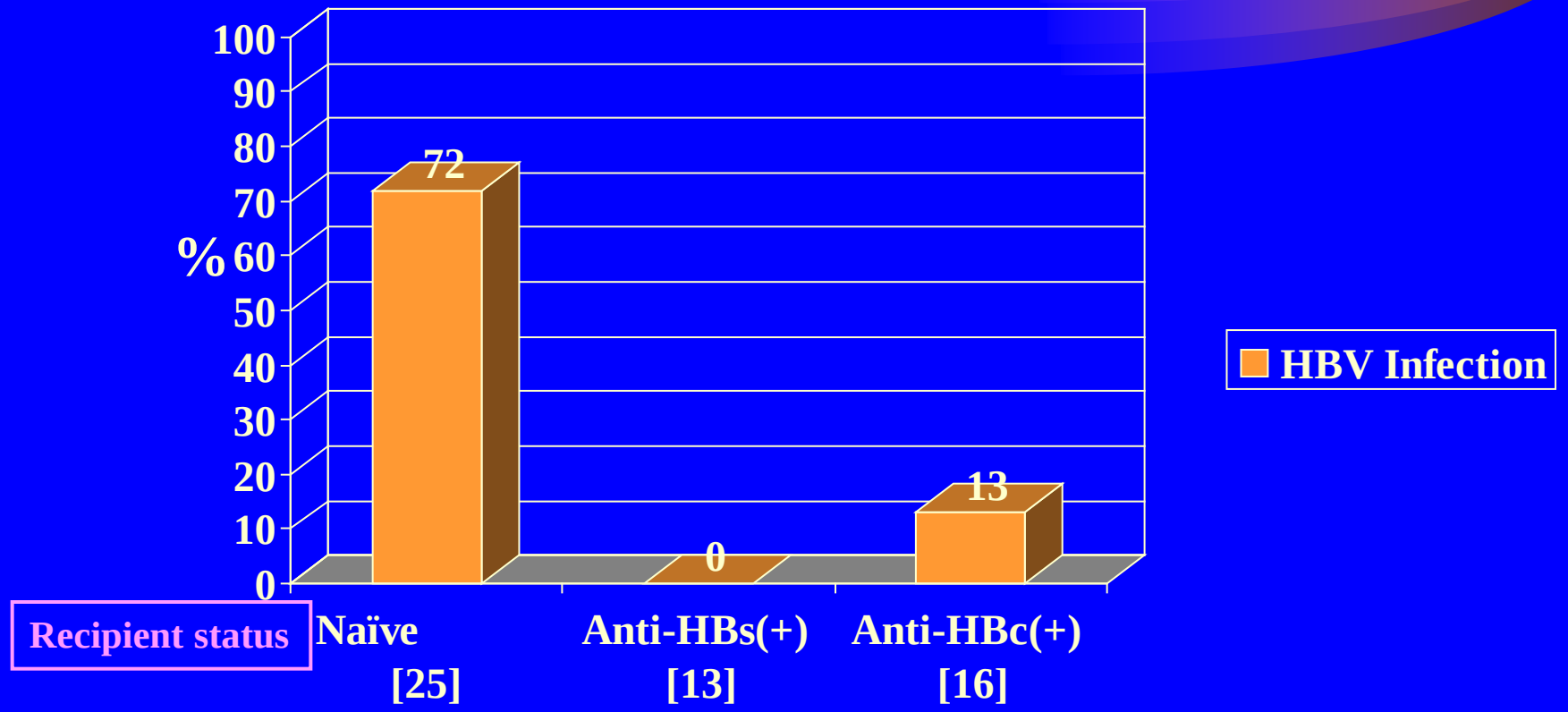
Risk of HBV acquisition

- Anti-HBc (+) or anti-HBs (+) donors: 33-100%
- Anti-HBc(+) organ given to:
  - HBV naïve recipient: 30-72%.
  - Anti-HBc(+) recipient: 13%.

Anti-HBc(+) Organ Donors

Risk of HBV Infection

Dodson et al. Transplantation 1997



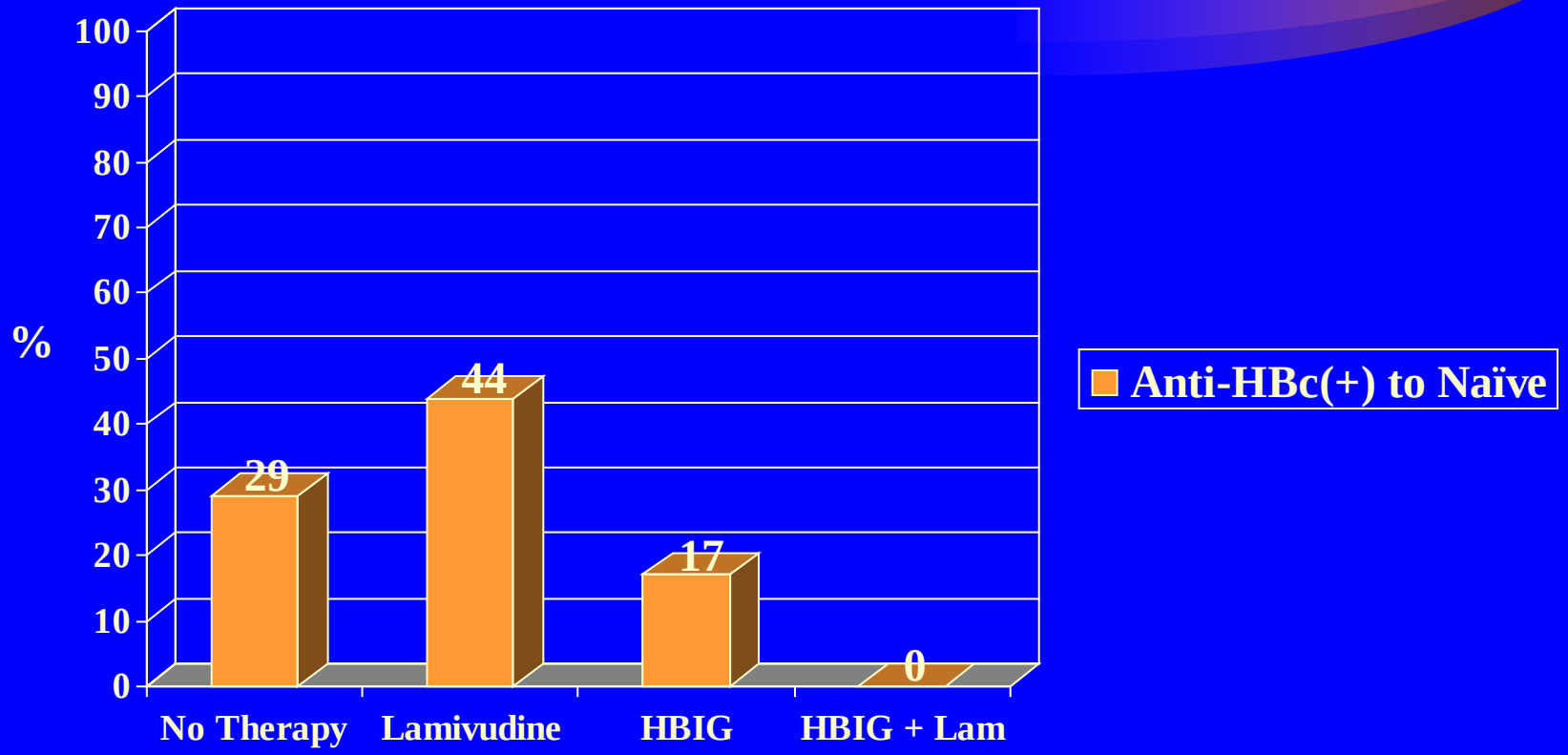
No HBV prophylaxis was given

Anti-HBc(+) Donor To Naïve Recipient

Effect of Prophylaxis

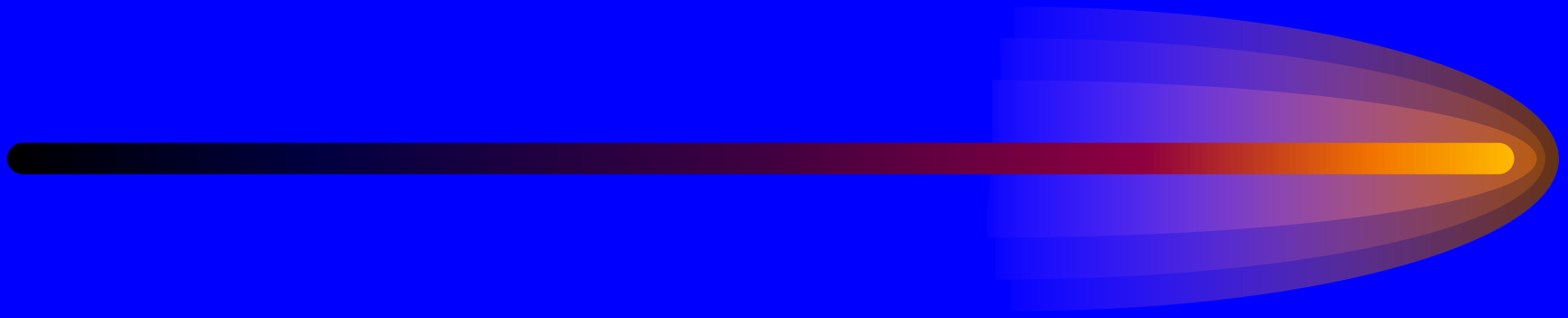
UCLA Experience

Ghobrial RM ; Transplant Hepatology CAQ Course - 2006



Prophylaxis for Anti-HBc(+) organ given to HBsAg(-) Recipient

Recipient Status	Donor Status	Oral Agent (adjust dose by renal function)	Immunization	Monitoring
Peak anti-HBs > 10 mIU/mL, or anti-HBc(+)	**Serum HBV-DNA(+) (found after LT)**	High "barrier-resistance", Entecavir, or Tenofovir] **for life.**	HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
Peak anti-HBs > 100 mIU/mL	Serum HBV-DNA(-)	Lamivudine 150 BID, until anti-HBs > 100 mIU/mL, or for life. Entecavir or Tenofovir are alternatives but costlier.	HBV-vaccine 40 mcg, until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
Peak anti-HBs 10-99 mIU/mL, or anti-HBc(+)	Serum HBV-DNA(-)	Lamivudine 150 BID, until anti-HBs > 100 mIU/mL, or for life Entecavir or Tenofovir are alternatives but costlier.	HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
anti-HBs < 10 mIU/mL, and anti-HBc(-)	**Serum HBV-DNA(+) (found after LT)**	High "barrier-resistance", Entecavir, or Tenofovir], **for life.**	HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life
	Serum HBV-DNA(-)	Lamivudine 150 BID, until anti-HBs > 100 mIU/mL, or for life. Entecavir or Tenofovir are alternatives but costlier.	HBV-vaccine 40 mcg @ 0,1,2,6 mo x 1-3 times until anti-HBs > 100 mIU/mL	HBsAg, HBe/anti-HBe, HBV-DNA quantitation q month x 3, and then q 3 months for life



HCV Recurrence Post Liver Transplant Natural History

Post-OLTx HCV Recurrence

- Infection occurs during graft reperfusion.
- Negative-strand HCV-RNA (replication) as early as 48h post-LTx.
- 25% have HCV core Ag in hepatocyte 10 d post-LTx, & > 90% @ 3 months post-LTx
- Pre-LTx HCV-RNA level may be reached by day 4.
- Peak titers reached at 1-3 mo post-Tx.
- 1-y post-LTX, HCV-RNA level are 10-100X pre-LTx
- Failure to develop a HCV-specific MHC-complex class II-restricted $CD4^+$ T-cell response contributes to graft-injury.

Acute HCV Recurrence

- Mild to moderate ALT/AST elevation
- Total bilirubin < 6 mg/dL
- Liver Bx in acute HCV:
  - mononuclear lobular infiltrate, variable hepatocyte necrosis, and fatty infiltration;
  - Il-2, IFN-gamma, and TNF gene expression dominate.
- Liver Bx in Acute Cellular Rejection:
  - endothelitis, severe bile duct damage, and *mixed-cell* infiltrate;
  - Il-4 & Il-10 gene expression dominate.
- Portal lymphocytic infiltrate and lymphocyte aggregates are seen in HCV & ACR.

Post-OLTx HCV Recurrence
Factors That Affect Outcome

- Pre-OLTx HCV-RNA > 600000 IU (1 M copies)
- Advanced Donor Age (> 50) (increase 1%/y after age 25; very poor if donor > 65 y)
- Treatment of ACR (do not treat mild rejection)
- High-average daily steroid dose
- T-cell depleting therapy
- CMV disease
- Non-caucasian recipient
- Year of OLTx (?); (worse in recent years)

Fibrosing Cholestatic Hepatitis

- Bilirubin > 6 mg/dL without biliary or vascular complications.
- Usually in 1st year
- Begins about 1 mo post LTx; liver failure in 3-6 months.
- ALT & AST elevated 2-5X; alk. phosph. > 500 U/L & GGT > 1000 U/L
- Very high serum (> 30-50 million IU/mL) & intrahepatic HCV-RNA

Fibrosing Cholestatic Hepatitis

- Liver Bx: severe perivenular hepatocyte ballooning, intrahepatic cholestasis, pericellular & portal fibrosis, ductular proliferation, and paucity of inflammation.
- Probably due to high immunosuppression; stable quasispecies; $T_H2 > T_H1$ cytokine response; direct cytotoxic injury.
- Prognosis: very serious illness with extremely high mortality.
- Treatment: Decrease immunosuppression; DAA therapy.

Chronic HCV Recurrence

- There is portal-portal bridging fibrosis and portal & lobular infiltration; variable degrees of hepatocyte necrosis.
- Progressive, non-specific Th^1 inflammatory response.
- Treatment traditionally recommended for stages METAVIR 2 / ISHAK 3 or higher, due to Interferon Toxicity.
- With current low toxicity drugs, therapy can be done earlier with very high SVR.

Post-OLTx HCV Recurrence

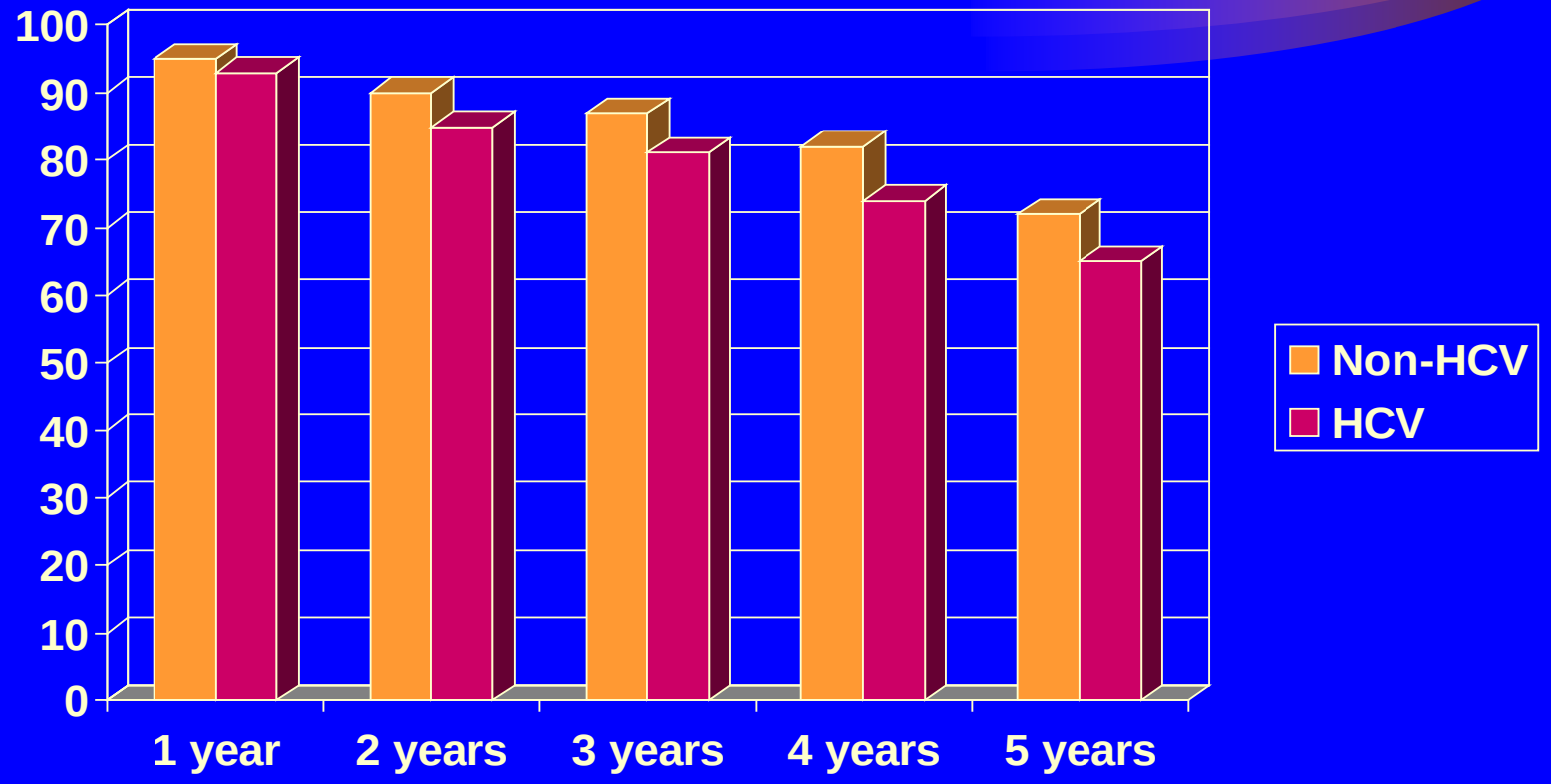
- Risk of death (hazard ratio 1.23) & of graft-loss (hazard ratio 1.3) is higher in HCV(+) than in HCV(-), at 1, 3, & 5 years; (but patient survival similar to ALD, & cryptogenic liver disease).
- Fibrosis progression in HCV:
  - **LTx = 0.3-0.8 stage/y vs**
  - **Immunocompetent = 0.1-0.2 stage/year.**
- Median time to cirrhosis:
  - **LTx = 10y;**
  - **Immunocompetent = 20-40 y.**

Post-OLTx HCV Recurrence

- Cirrhosis:
  - **6-23% in 3-4 y,**
  - **30% by 5 y.**
- Risk of decompensation:
  - **1y = 42% (< 5% immunocompetent) &**
  - **3y = 62% (< 20% in Immunocompetent)**
- Approximately 10-25% of post-LTx HCV-liver disease will need re-Tx or will be dead within initial 5 years.

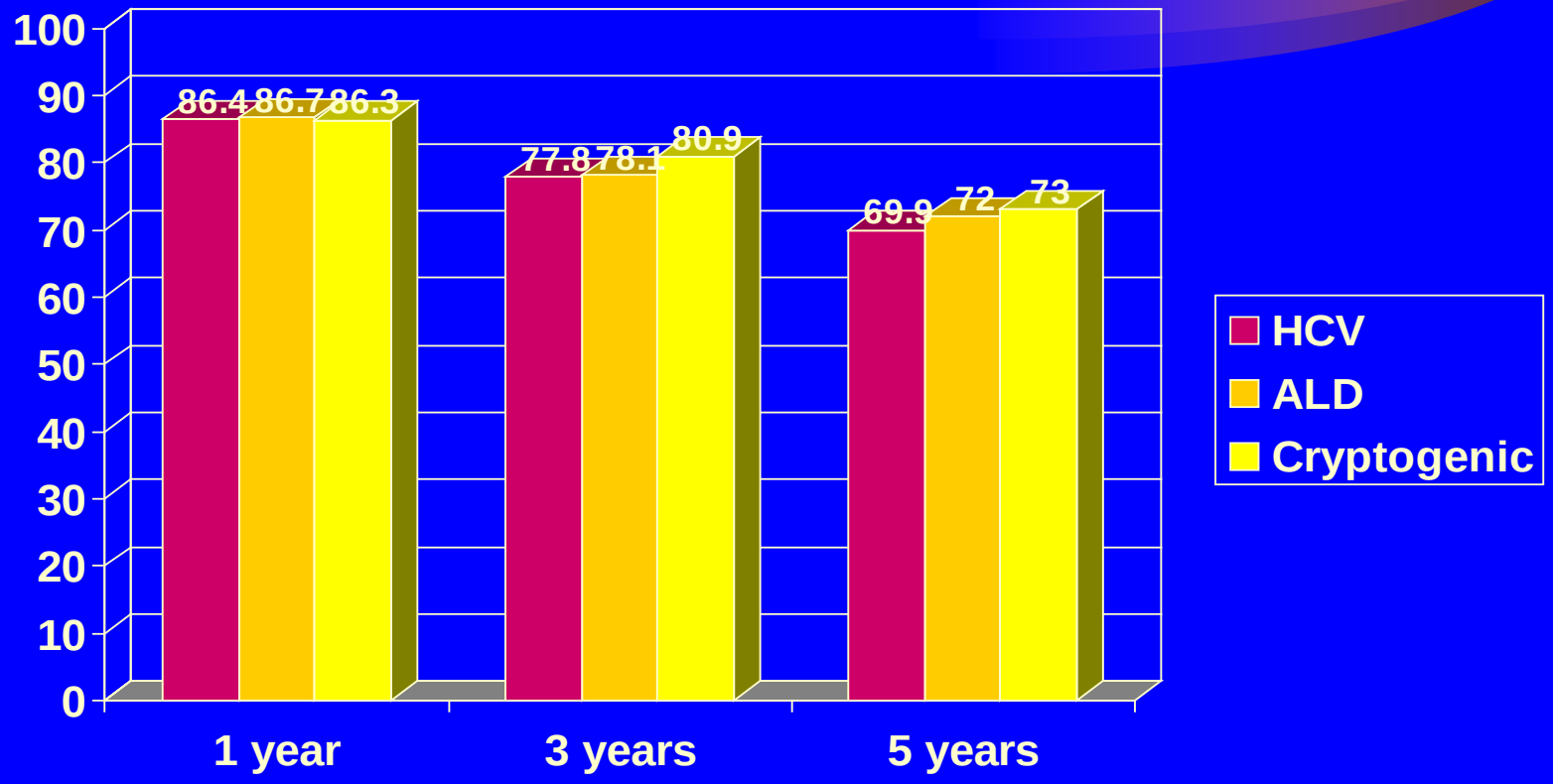
Survival After Liver Transplantation

UNOS (1992-98) Gastroenterol 2002;122:889-896



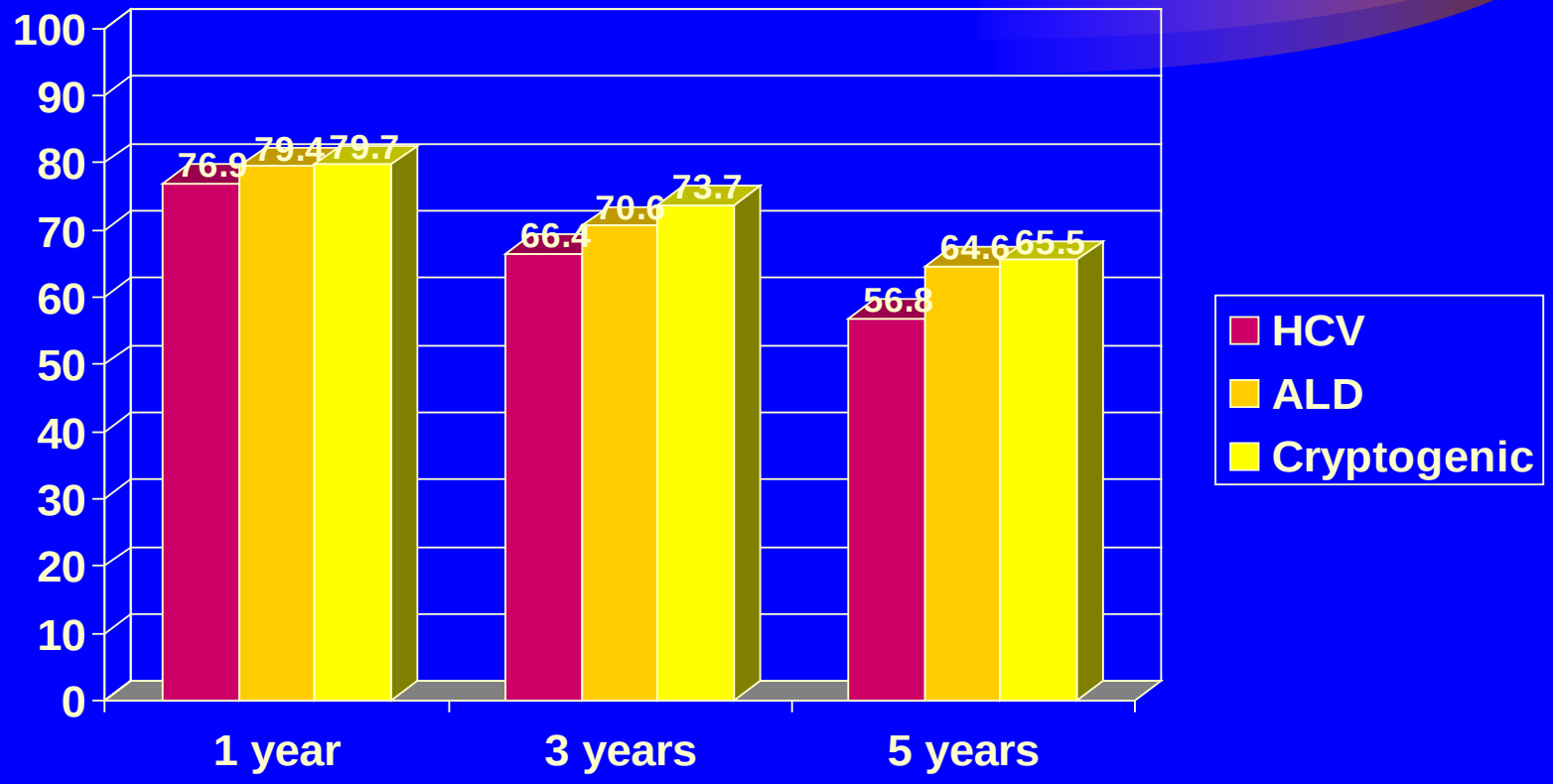
Patient Survival After Liver Transplantation

UNOS (1992-98) Gastroenterol 2002;122:889-896



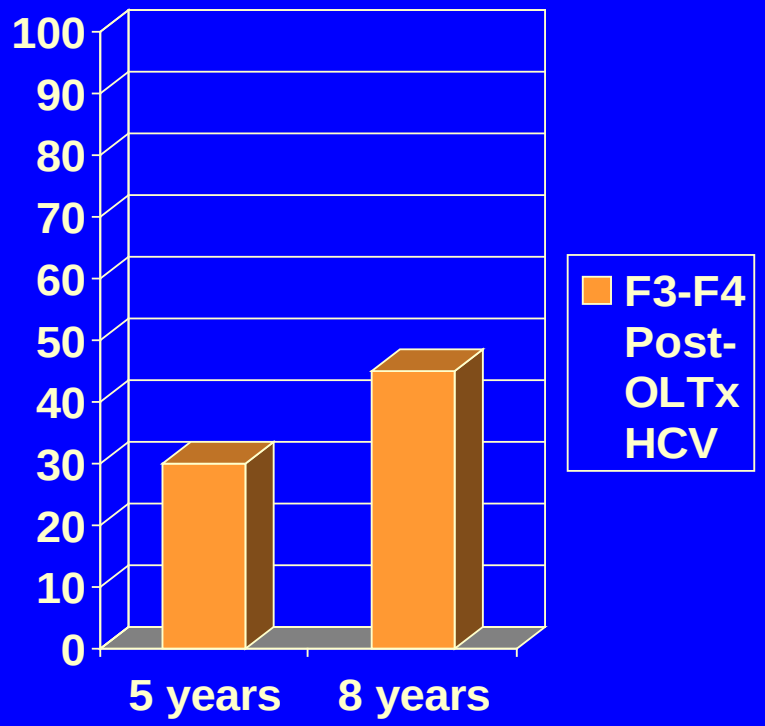
Graft Survival After Liver Transplantation

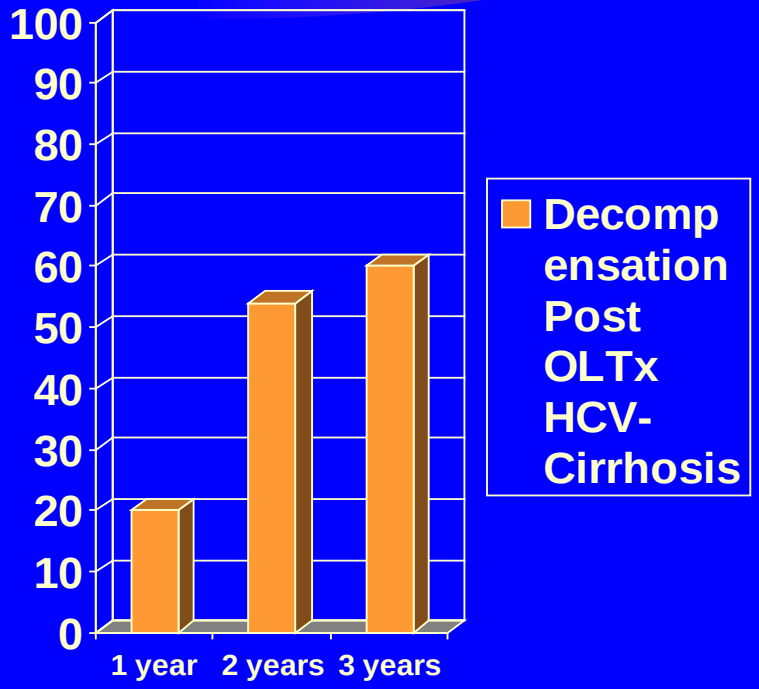
UNOS (1992-98) Gastroenterol 2002;122:889-896



Progression to F3-F4 Fibrosis and to Decompensated Cirrhosis Post OLTx HCV

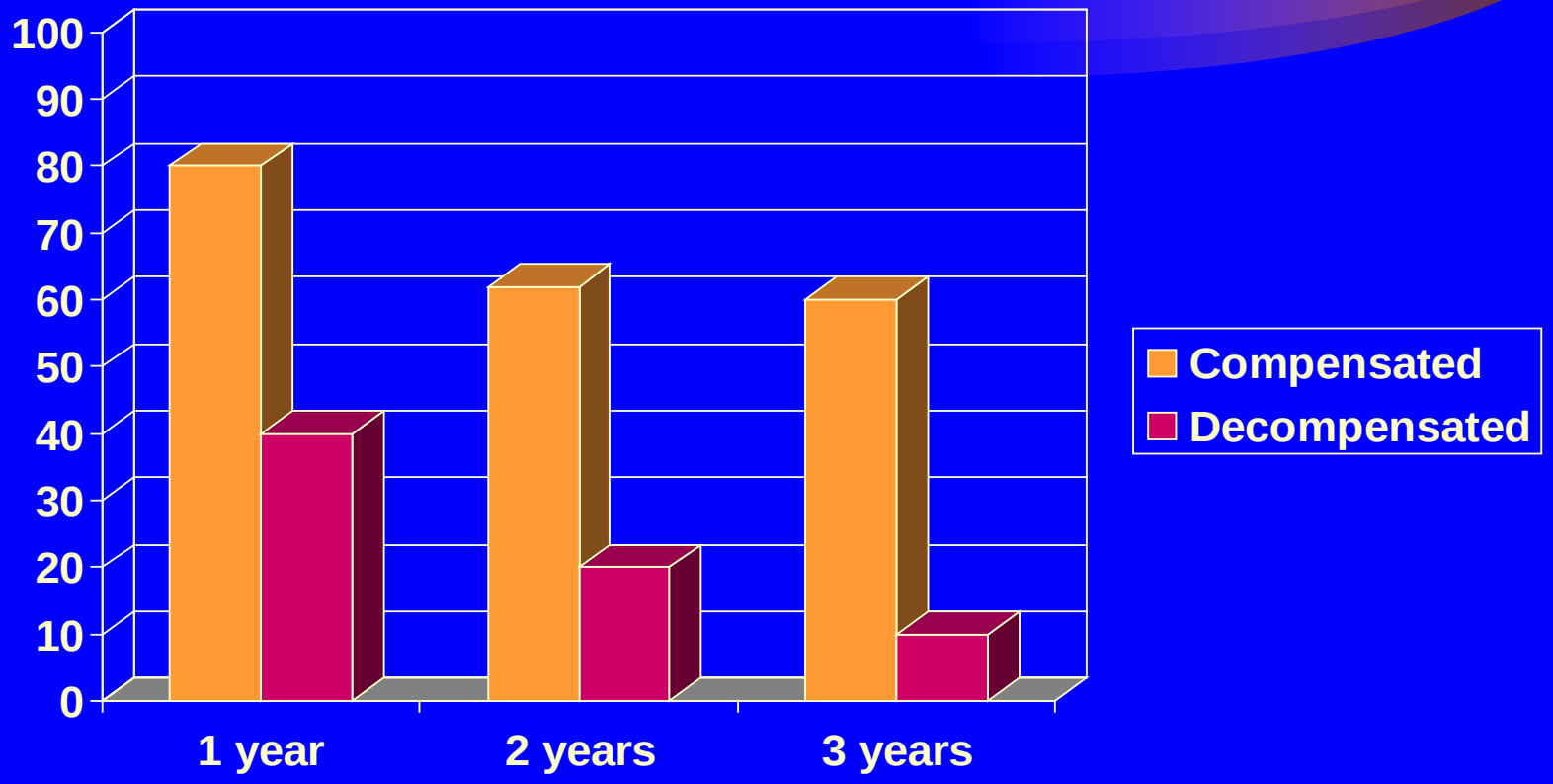
Berenguer et al J. Hepatol 2000;32:673-684 & Hepatology 2000;32:852-858





Survival in Post-OLTx HCV-Cirrhosis

Berenguer et al. Hepatology 2000;32:852-858



Peg-IFN Treatment of Recurrent HCV After METAVIR Stage 2

- Interferon or RBV monotherapy have not improve fibrosis nor induce SVR.
- With Peg-IFN + RBV, SVR has been 26-45%
- 60% of patients with SVR improve histology; 20 % remain stable.
- 30-60% require RBV dose reduction; 30% need discontinuation of therapy.
- There is no increase in rate of Acute nor Chronic Rejection.

Histologic Scoring of Fibrosis

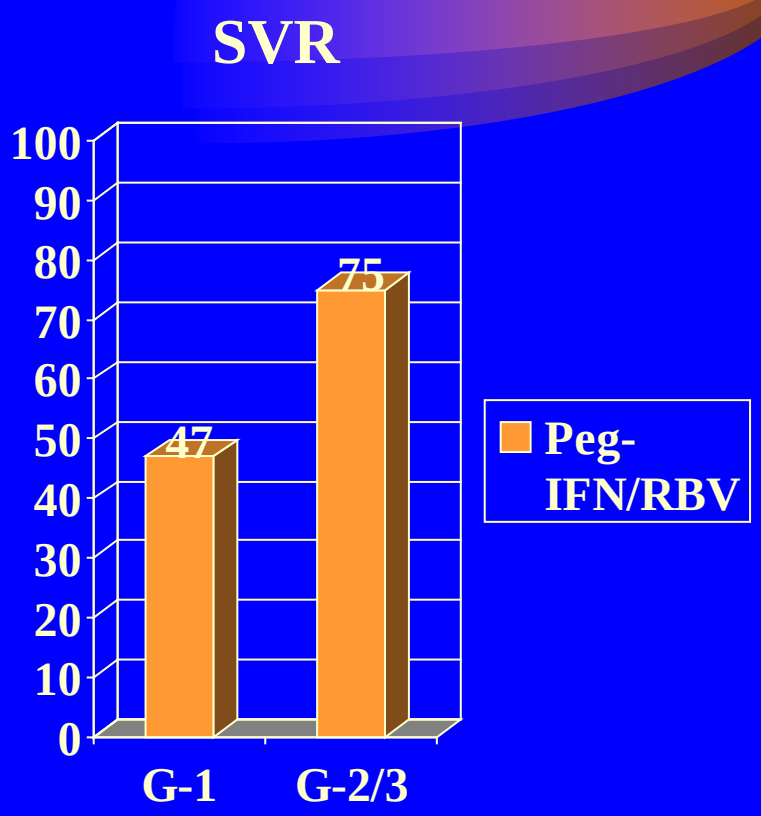
FIBROSIS	METAVIR	Ishak
None	0	0
Portal fibrosis (some p. areas)	1	1
Portal Fibrosis (most p. areas)	1	2
Bridging fibrosis (occasional)	***2***	***3***
Bridging fibrosis (marked)	**3**	**4**
Incomplete cirrhosis	**4**	**5**
Cirrhosis	**4**	**6**

Treat METAVIR =/> 2, or Ishak =/> 3

Peg-IFN + RBV for HCV Recurrence in OLTx Recipients

Berenguer M et al. Liver Transpl 12:1067-1076, 2006

- 36 patients
- Median time OLTx-Rp = 513 d
- Cirrhosis 15%, cholestatic HCV 9%
- 88% off steroids
- Premature D/C 40%
- ADEs 57%
- Rejection 14%
- EPO increased SVR
- HCV-RNA drop < 2 log @ 12 wks = non-response



Treatment After Liver Transplant

Genotype	Regimen	Duration (weeks)	SVR
1	F0-4: **SOF/LED 400/90 + RBV 1-1.2 g** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day)	**12**	96%
	F0-4: **SOF/LED 400/90**	**24**	?
	F0-4: **SOF 400 + DCV 60 +/- RBV 600-1000**	**12** (with RBV) **24** (without RBV)	1a: 97% 1b: 90%
	Only in F0-2: **PrOD + RBV 1-1.2 (alt)** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day) [CSA :1/5 of usual dose when starting Viekira and follow daily levels; TAC do not give on 1st day of Viekira; monitor levels and then give 0.5 mg/week as determined by levels]	**24**	1a: 97% 1b: 100%
	F0-4 comp: **SOF 400 + SIM 150 +/- RBV 1-1.2 g (alt)** (not in genotype 1a with Q80K mutation)	**12**	92%
4	**SOF/LED 400/90 + RBV 1-1.2 g** (RBV: in decompensated, increase dose weekly if tolerated; start with 600 mg/day)	**12**	96%
	SOF/LED 400/90	**24**	?
	SOF 400 + DCV 60 + RBV 600-1000	**12** (with RBV) **24** (without RBV)	91%

(alt) = alternative regimen due to more toxicity or slightly lower efficacy

Treatment After Liver Transplant

Genotype	Regimen	Duration (weeks)	SVR
2	**Sofosbuvir (400 mg) and RBV 1-1.2 g** (RBV: if decompensated, start with 600 mg/day, and increase weekly as tolerated up to 1000 mg/day [<75 kg] or 1200 mg/ day [≥75 kg] 1200 mg depending on Clcr and hemoglobin).	**24**	?
	DAC 60 + SOF 400 +/- RBV 600-1200 (F0-4 comp)	**12** (with RBV) **24** (without RBV)	?
	SOF/LED 400/90 if intolerant to RBV (no FDA approved)	**12**	?
3	**Sofosbuvir (400 mg) and RBV 1-1.2 g** (RBV: if decompensated, start with 600 mg/day, and increase weekly as tolerated up to 1000 mg/day [<75 kg] or 1200 mg/ day [≥75 kg] 1200 mg depending on Clcr and hemoglobin).	**24**	?
	SOF 400 + DCV 60 + RBV 600-1200 mg	**12** **24** without RBV **24** with RBV for fibrosing cholestatic hepatitis	91%
	SOF/LED + RBV (?) no enough data (no FDA approved)		?

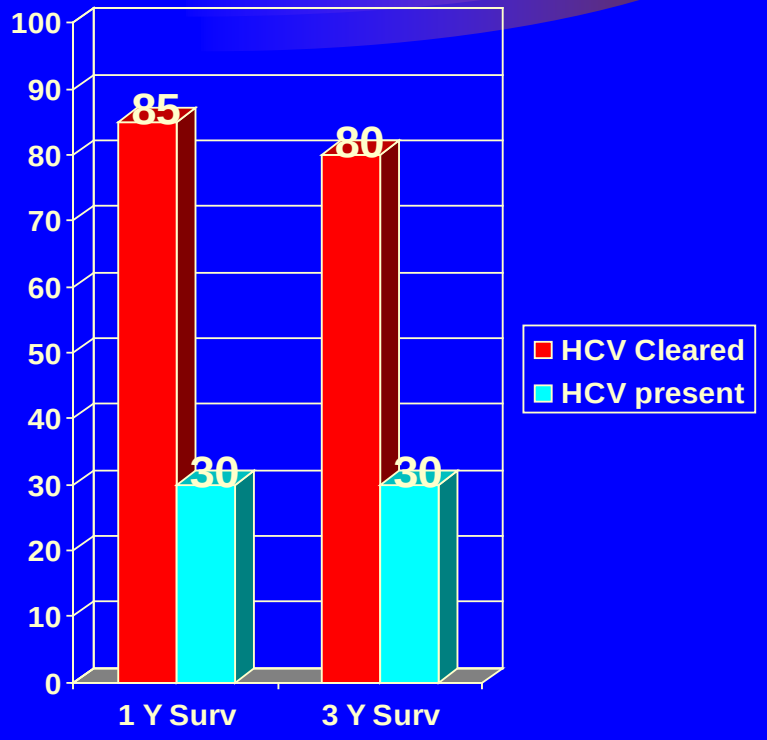
Predictors of Poor Outcome in HCV Re-Transplantation

- Bilirubin > 10 mg/dL
- Creatinine > 2 mg/dL
- Creatinine clearance < 40 mL/min
- Recipient > 55 years
- Cirrhosis < 1 year post-LTx
- Donor > 40 years

Re-transplantation for Graft Failure in HCV patients - Effect of Viral Clearance

Sharzehi K et al. AASLD Abstr 500, 2009

- Patients: 32 HCV infected s/p OLTx who developed graft failure and needed re-transplantation.
- Mean time to re-transplant: 41 months
- Indications: ch. rejection 37%, HCV infection 28%, both 31%
- Causes of death post re-OLTx: Sepsis 25%, HCV 15%, MOF 6%
- Treatment against HCV given to 56%; 38% of them had SVR



Recurrent PBC

Neuberger J. Liver Transplantation 2003

- **Rate**:
  - 17% with strict criteria;
  - 26% with expanded criteria
- **Diagnostic Criteria**:
  - OLTx for PBC, and
  - AMA persistence, and
  - Histology (2/4 = probable; 3/4 = definitive)
    - Mononuclear cell infiltrate
    - Lymphoid aggregates
    - Epitheloid granulomas
    - Bile duct lesions

Recurrent PBC

Risk Factors

Risk Factor	Impact
Little mismatch of HLA-A, HLA-B, and HLA-DR	**Increased**
Living donor recipient	**Increased**
Tacrolimus	Increased ?
Warm/cold ischemia time	Increased ?
Young donor/recipient	Increased ?
Steroid discontinuation	Unclear

Recurrent PBC

Treatment & Prognosis

- UCDA commonly used; decreases alkaline Phosph & ALT in 52% @ 36 month.
- No change in graft nor patient survival.
- Infrequent need for late re-transplantation (4% from recent UNOS database)

Recurrent PSC
Diagnostic Criteria
Graziadei I. Liver Transplantation 2002

- OLTx for confirmed PSC
- Absence of Exclusion Criteria
- Cholangiography
  - Intrahepatic and/or extrahepatic strictures/ beading/ irregularities > **90 days after OLTx**
- Histopathology
  - Fibrous cholangitis and/or fibro-obliterative lesions +/- ductopenia, fibrosis, or cirrhosis

Recurrent PSC
Exclusion Criteria
Graziadei I. Liver Transplantation 2002

- Hepatic artery thrombosis or stenosis.
- Chronic ductopenic rejection
- Anastomotic stricture alone.
- Non-anastomotic stricture < 90 days post-OLTx
- Donor/ Recipient ABO incompatibility.

Recurrent PSC
Predictors, Prognosis, & Therapy

- **Incidence:** 10-27% ; onset: 6 mo 5y.
- **Predictors**:
  - UC with intact colon,
  - Steroid resistant rejection,
  - Albumin given at OLTx,
  - HLA-DR matching, and/or HLA-DRB1*08
  - Cholangio-Ca before OLTx.
- **Prognosis**:
  - 7.5% re-transplantation rate.
- **Treatment**:
  - none proven;

Recurrent AIH

Suggested Diagnostic Criteria

- OLTx for AIH
- Persistence of autoantibodies
- Hypergammaglobulinemia and/or high IgG
- Characteristic Histology
  - Prominent portal interface hepatitis
  - Lymphoplasmocytic infiltrate
  - Lobular involvement
  - Occasional: bile-duct lesion, endothelialitis.
- Response to Steroids
- Exclusion of other causes.

Recurrent AIH

Risk Factors

- Discontinuation of steroids; low-dose immunosuppression.
- Type-I AIH = 34%; Type-II AIH = 5%
- HLA-DR3/DR-4 recipient ?
- Severe necroinflammatory activity ?
- Unaffected by Tacrolimus vs CyA

Recurrent AIH

- Incidence: 23% (patients should stay with steroids in immunosuppressant protocol).
- Interval to Dx: 26.4 mo (14-55)
- Autoantibodies: most commonly ANA >/= 1:40, anti-SLA. May have (+) ASMA, anti-LKM1, ANCA.

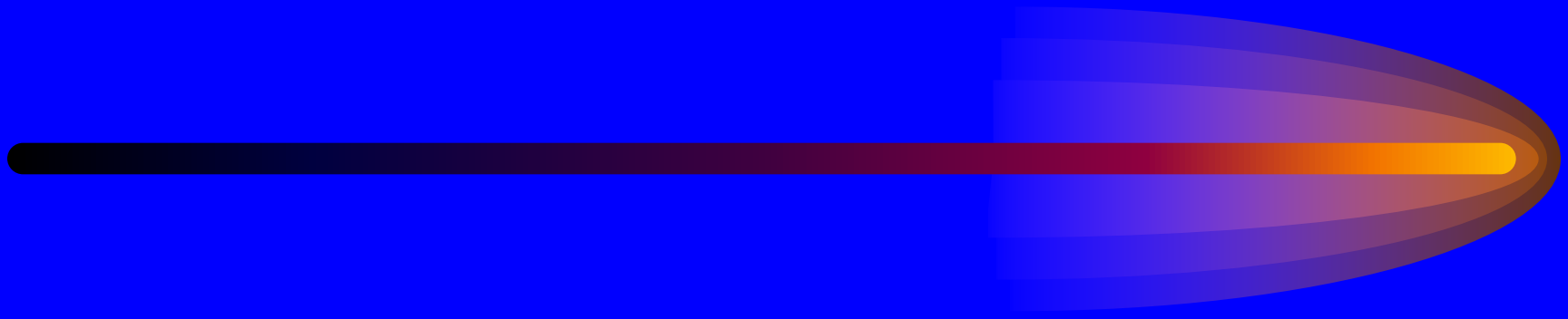
Recurrent AIH

Treatment & Prognosis

- Prednisone +/- Azathioprine
- Switch from CyA to Tacrolimus potentially effective.
- Sirolimus in non-responders to steroids.
- Graft & patient survival unaffected at medium-term.
- Long-term progression to cirrhosis: 40%.
- May need re-transplantation.
- **Rarely recurs in new allograft.**

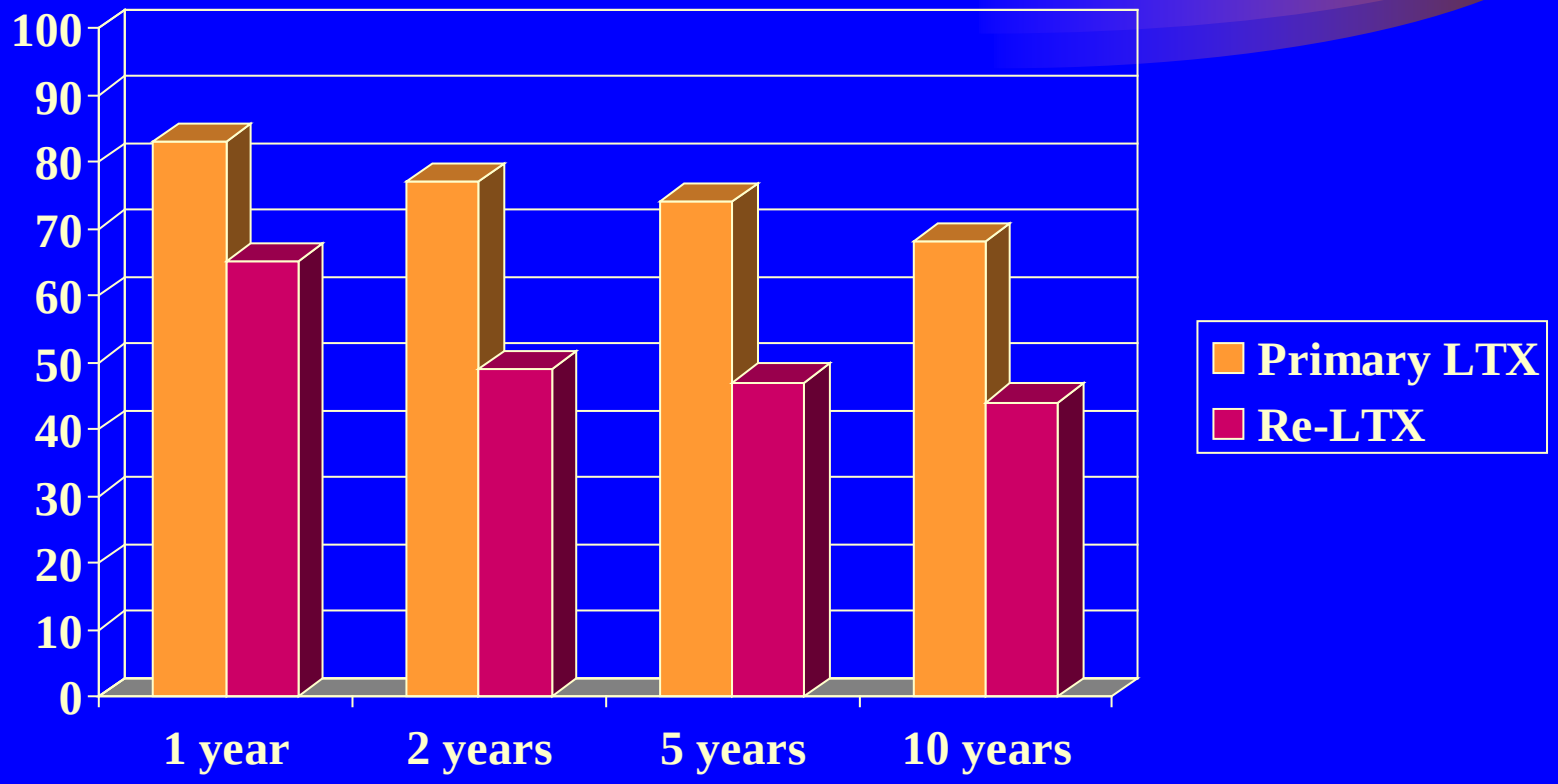
Recurrent NASH

- Found in “Protocol Biopsies”
- Clinical evidence of weight gain, hyperglycemia, hypertriglyceridemia.
- At 1 year: NASH in 25%
- At 4 years: NASH in 50%



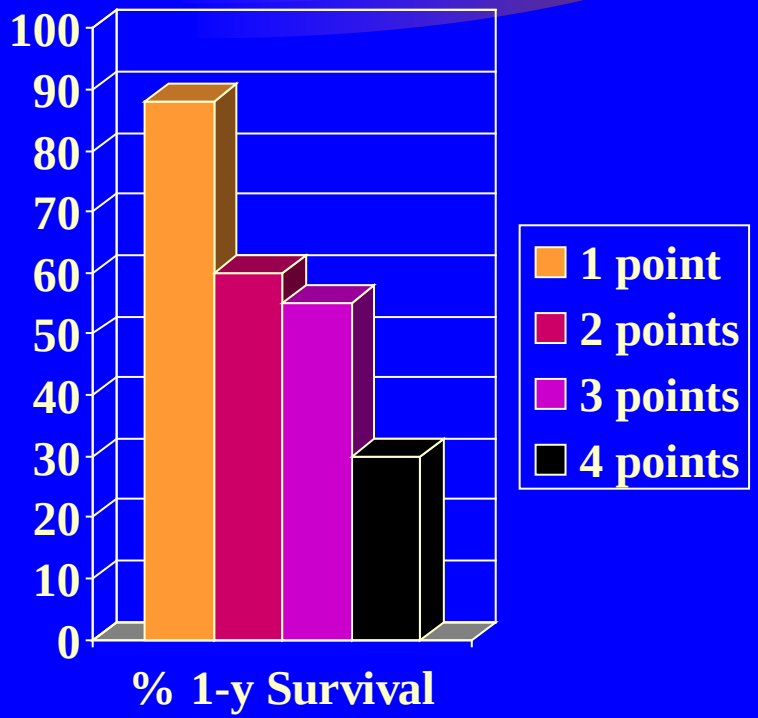
Re-Transplantation

Survival after Liver Transplant & Re-Transplant



Re-LTX 1-year Survival by UCLA Class

- **POINTS (1 each)**
- Age > 18
- Liver ischemia > 12 h
- Pre-op in ventilator
- Creatinine > 1.6mg/dL
- Bilirubin > 16mg/dL



Long-Term Follow-Up

- Labs:
  - CBC + diff
  - CMP
  - CSA or tacrolimus levels
- Vaccines:
  - ***Yes***: HBV, pneumococcus, influenza
  - ***No***: live/attenuated → measles, mumps, rubella, oral polio, BCG

Long-Term Follow-Up

- **Metabolic Syndrome:** any 3 of the following
  - Abdominal girth: males > 40 in, female > 35 in
  - Lipid panel after 14 h fasting:
    - Triglycerides > 150 mg/dL
    - HDL: < 40 mg/dL in males, < 50 in females
    - LDL > 100 mg/dL
  - Fasting blood sugar >/= 100 mg/dL
  - BP > 130/85 mm Hg

Long-Term Follow-Up

- **Hyperlipidemia:**
  - Hyperlipidemia with Sirolimus > CSA > Tacrolimus.
  - Change to Tacrolimus, minimize dose, or change to MMF regimen.
  - Mediterranean diet.
  - Best choice is Pravastatin 20 mg; others are simvastatin 40 mg, or atorvastatin 40 mg

General Plan for the Stepwise Management of Dyslipidemia

- Elevated low-density lipoprotein cholesterol level > 100 mg/dL (with or without elevated triglycerides)
  - 1. Therapeutic lifestyle and dietary changes
  - 2. Statins
  - 3. Addition of ezetimibe
- Hypertriglyceridemia with normal cholesterol
  - 1. Fish oil at 1000 mg twice daily to 4 g daily if tolerated
  - 2. Fibric acid derivatives
- Refractory hyperlipidemia: consider changes in
- immunosuppression
  - 1. Conversion of cyclosporine to tacrolimus
  - 2. CNI reduction (eg, add mycophenolate mofetil)
  - 3. Discontinuation of sirolimus

Long-Term Follow-Up

- **Hypertension:** (BP > 130/80 mm Hg).
  - Goal: 125/75 for renal impairment; others 130/80
  - Steroid reduction or withdrawal, change CSA to tacrolimus, change CNI to sirolimus, or MMF.
  - Best are Ca channel blocker (amlodipine or nifedipine, that decrease vasoconstriction from CNI), plus diuretics
  - Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors should be used as first-line antihypertensive therapy in LT recipients with DM, CKD, and/or significant proteinuria (grade 1, level A); addition of diuretics mitigate volume retention from CNI.

Long-Term Follow-Up

- **Insulin Resistance** (HOMA >/= 2.5)
  - Avoid, or tapper & discontinue steroids rapidly (within 3 months).
  - Tacrolimus depletes pancreatic beta-cell mRNA; change to CSA
  - ADA weight control Diet + Exercise >/= 4000 steps/d
  - Metformin if creat </= 1.5 mg/dL in males, & 1.25 in females.
  - Glinides: repaglinide (Prandin).

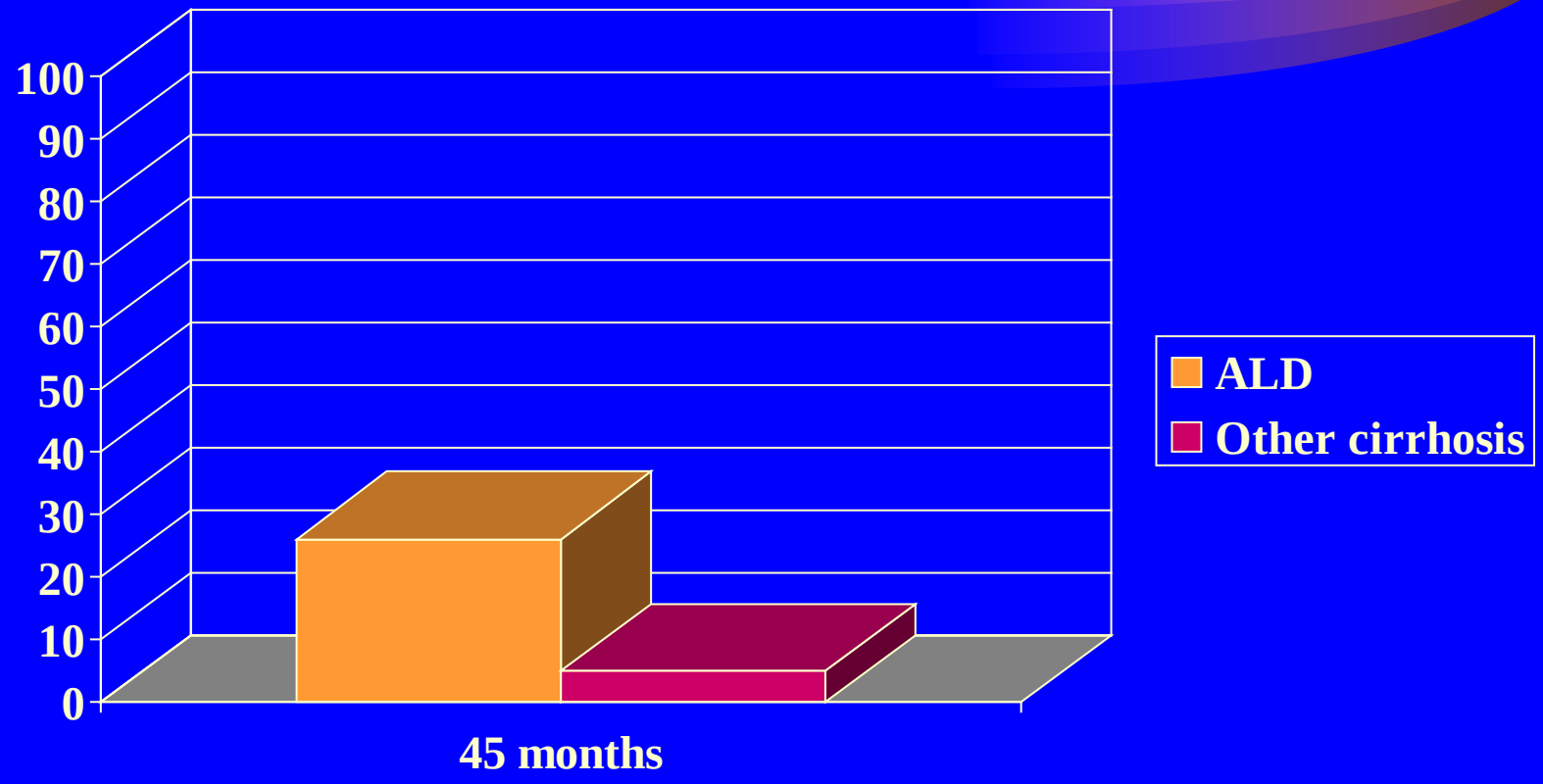
Long-Term Follow-Up

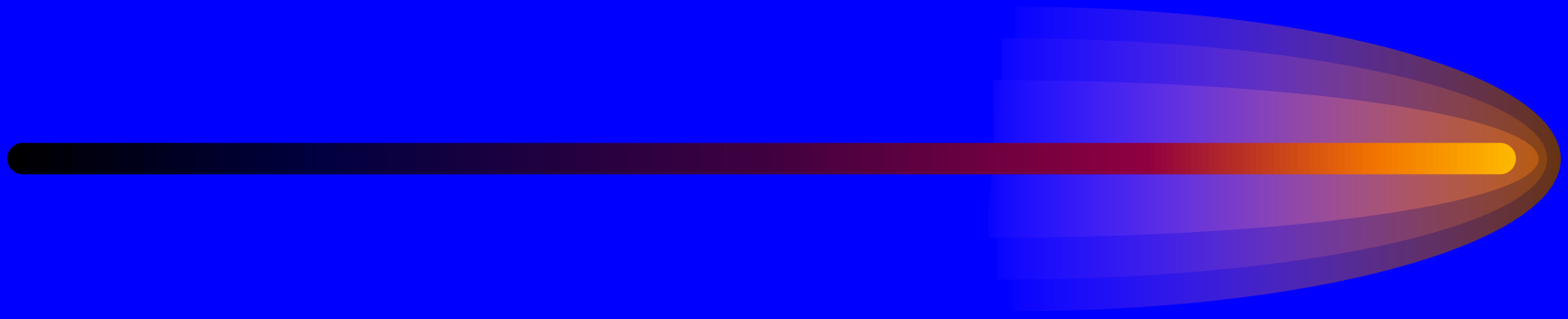
- **Dental:**
  - Periodontal prophylaxis every 6 months
- **Bone:**
  - Calcium = 1200 mg/d
  - Vitamin D = 400-800 IU/d
  - Bone densitometry (DXA)

Long-Term Follow-Up

- **Colorectal:**
  - **Colonoscopy every 10 years** (>50 y/o)
  - In U.C. → colonoscopy every year
- **Contraception** → High Risk Pregnancies

Long-Term Follow-Up
Risk of oro-pharyngeal Neoplasm





Questions ?

Combination HBIG + Oral agent
High Replicators ***(> 10^4 copies or > 2000 IU/mL)***

- **Anhepatic phase**: HBIG 10000 IU IV
- Continue effective "high resistance-barrier" oral agent, post-OLTx, **for life**.
  - Give either (Adefovir + Lamivudine), Entecavir, Tenofovir, or combination regimen that was effective pre-Tx.
- **First week**: daily 10000 IU HBIG IV x 6 days
- **Thereafter: 936** IU IM q month (3 mL Nabi-HB), starting on day 7 post-op.
- **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.

Combination HBIG + Oral agent

Low replicators** (</=10^4 copies/mL or < 2000 IU/mL), **Fulminant HBV, and HBV+Delta

Angus PW. Liver Transpl 2000;6:429-433; Gane EJ. Gastroenterology 2007;132:931-937

- **Anhepatic phase**: HBIG 936 IU IM (3 mL Nabi-HB)
- Start/continue “high resisrance-barrier”oral agent post-OLTx **for life**:
  - Either (Adefovir + Lamivudine), Entecavir, or Tenofovir, or the combination that was effective before transplant.
- **First week**: daily 936 IU HBIG (3 mL Nabi-HB) IM x 7 days.
- **Thereafter**: HBIG 936 IU IM q month (3 mL Nabi-HB)
- If after 1 year HBV-DNA is still “non-detectable”, consider to discontinue HBIG after vaccination + boosters (40mcg @ 0,1,2 & 6 mo) x 1-3 courses, if patient responds with anti-HBs > 100 mIU/mL.
- **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.

Definitions for Oral Antivirals

Pre-OLTx anti-HBV Therapy

- **High replicators** > 10^4 copies/mL or > **2000 IU/mL**:
  - high risk for graft re-infection and death;
  - all cirrhotics with > 10^4 copies/mL (2000 IU/mL) need therapy with “high resistance-barrier agent” (Tenofovir, Entecavir, or Lamivudine+Adefovir).
- **Low replicators** < 10^4 copies/mL (**< 2000 IU/mL**):
  - moderate/low risk re-infection & death;
  - if < 10^2 copies/mL, may be candidates for post-OLTx [short-term HBIG + oral agent], or [oral “high resistance-barrier” agent monotherapy].

Definitions for Oral Antivirals
Pre-OLTx anti-HBV Therapy

- **Primary non-response**: drop of HBV-DNA < 1 log after 12 wks of therapy
  - Check for viral resistance (INNO-Lipa HBV DR v2). May be compliance issue, or host pharmacologic effect.
  - Change or **add second drug without cross-resistance**.
- **Partial Response**: HBV-DNA > 2000 IU/mL after 24 weeks of therapy.
  - Predicts high risk for resistance. (Resistance risk is low if HBV-DNA is < 200 IU/mL).
  - Change or **add second drug without cross-resistance**.
- **Breakthrough**: increase of HBV-DNA > 1 log from nadir, at any time, or reappearance of HBV-DNA(+) after 2 negative HBV-DNA at least 1 month apart.
  - Check for viral resistance (INNO-Lipa HBV DR v2). May be compliance problem.
  - Change or **add second drug without cross-resistance**.

Drug Cross-Resistance Profile

(reverse transcriptase mutations)

Zoulim F et al. J of Hepatology 2008;48: S2-S19

	Lamivudine	Telbivudine	Entecavir	Adefovir	Tenofovir
Wild	**S**	**S**	**S**	**S**	**S**
M204I	**R**	**R**	**R**	**S**	**S**
L180M + M204V	**R**	**R**	**I**	**S**	**S**
A181T/V	**I**	**S**	**S**	**R**	**S**
N236T	**S**	**S**	**S**	**R**	**I**
I169T + V173L + M250V	**R**	**R**	**R**	**S**	**S**
T184G + S202I/G	**R**	**R**	**R**	**S**	**S**
I233V				Resistance ?	
A194T					Resistance ?

Treatment Options for Antiviral Resistance

Resistance to	Rescue Therapy
Lamivudine or Telbivudine	**Add:** Adefovir, or Tenofovir, or **Switch to:** Tenofovir + Emtricitabine (Truvada)
Adefovir	**Add:** Lamivudine, or Entecavir, or **Switch to:** Tenofovir + Emtricitabine (Truvada)
Entecavir	**Add:** Adefovir, or Tenofovir
Multidrug	**?**

Anti-HBc(+) liver donors

- **Primary candidates:**

HBsAg(+) recipients

– Follow protocols for Low, or High Replicators as described in previous section (“HBsAg(+) Recipient”).

Anti-HBc(+) organ donors

- **<u>Secondary candidates</u>:**

1) anti-HBs(+) recipients (with titer > 10 IU/L),
2) anti-HBc(+) recipient

– **Before OLTx or other Tx:**

- Order HBV-DNA in donor's serum (to detect "pre-S/S mutant virus" = HBsAg(-) mutant), and
- Check or order recipient's "peak" anti-HBs titer (if not known, obtain pre-op anti-HBs titer)

Anti-HBc(+) organ donors

– **Secondary candidates management:**

– **Donor's serum HBV-DNA (+) & any Recipient's peak anti-HBs titer (**despite absence of HBsAg)**:**

- Highly active, "high resistance-barrier", oral agent (Lamivudine+Adefovir combination, or Tenofovir or Entecavir) **for life**;
- Booster vaccinate after 1 year, if HBV-DNA is still (-), with HBV-vaccine 40mcg @ 0,1,2 & 6 mo x 1-3 courses, until anti-HBs > 100 IU/mL (but continue oral agent for life; likely "pre-S/S mutant virus")

Anti-HBc(+) organ donors

- **Secondary candidates management**:

- **Donor's serum HBV-DNA (-) & Recipient's peak anti-HBs titer > 100 IU/L:**
  - Lamivudine 150 mg BID (until anti HBs > 100 mIU/mL, or for life).
  - Booster vaccinate x 1 dose and check anti-HBs.
  - Discontinue oral agent after 1 year if good anti-HBs response is maintained (> 100 mIU/mL) ?
- **Donor's serum HBV-DNA (-) & Recipient's peak anti-HBs titer is < 100 IU/L:**
  - Lamivudine 150 BID (until anti HBs > 100 mIU/mL, or for life).
  - Booster vaccinate after 1 year, if HBV-DNA is still (-), with HBV-vaccine 40mcg @ 0,1,2 & 6 mo x 1-3 courses, until anti-HBs > 100 mIU/mL.
  - Discontinue oral agent after 1 year if good anti-HBs response is achieved (> 100 mIU/mL) ?

Anti-HBc(+) organ donors

- **Secondary candidates management**:

- **Choice of oral agent**:
  - If donor HBV-DNA in serum is (+) give Tenofovir or Entecavir.
  - If donor HBV-DNA in serum is negative, give Lamivudine 150 mg BID (corrected by renal function).
- **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.

Anti-HBc(+) organ donors

- **Tertiary candidates:**

- **HBV naïve patients [anti HBc(-) & anti-HBs(-)]**
  - Before OLTx, check/order HBV-DNA in donor's serum.
  - **If Donor's serum HBV-DNA is (+) :**
    - High resistance-barrier oral agent (Entecavir, or Tenofovir) **for life**; [to give HBIG will not help if donor's HBsAg was (-); likely "pre-S/S mutant virus"]
    - Vaccinate after 1 year, if HBV-DNAis still(-).
    - Independently of anti-HBs response, give oral agent for life.
  - **If Donor's serum HBV-DNA is negative**:
    - Lamivudine 150 mg BID for life.
    - Vaccinate after 1 year, if HBV-DNAis still (-), with HBV-vaccine 40mcg @ 0,1,2 & 6 mo x 1-3 courses, until anti-HBs > 100 mIU/mL.
    - Discontinue oral agent after 1 year if good anti-HBs response is achieved (anti-HBs > 100 mIU/mL) ?

Anti-HBc(+) organ donors

- **Tertiary candidates:**

– **Choice of oral agent**:
  - If HBV-DNA in serum is (+) give Tenofovir or Entecavir.
  - If HBV-DNA in serum is negative, give Lamivudine.

– **Monitoring**:
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q month x 3; then
  - HBsAg, HBe Ag & Ab, and HBV-DNA quant q 3 months for life.

Risk Factors Associated to Severity of Recurrence

- **Recipient related**
  - **Female gender:** **lower survival**
  - **Age:** **lower survival**
  - **Non-white race:** **lower survival, more severe**
  - **Severity of illness:** **lower survival**
  - *Hepatitis B co-infection:* *controversial*
- **Donor Related**
  - **Age:** **lower survival, more severe**
  - *HLA-mismatch* *controversial*
  - *Living donor:* *controversial*
  - *Donor-liver fat:* *controversial*
  - *Genetic factors:* *controversial*

Risk Factors Associated to Severity of Recurrence

- **Virological**
  - **Pre-LTx viral load (>1M):** **more severe**
  - **Early post-LTx load:** **more severe**
  - **CMV infection (+ g-1a):** **more severe**
  - **HIV co-infection:** **more severe**
  - *Genotype 1b:* *controversial*
  - *Quasispecies:* *controversial*
- **Other**
  - **Time to recurrence:** **more severe**
  - **Steroid bolus, OKT3:** **more severe**
  - **Short time to recurrence:** **more severe**
  - *Cold ischemia time:* *controversial*