Hepatitis C and Liver Transplantation

Dinesh Ranjan, M.D.
Professor of Surgery
Director of Liver Transplantation
University of Kentucky

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History

- Known as Non-A Non-B Hepatitis in 1974
- HCV identified in 1989
  - Virus: Flaviviridae family
  - 6 genotypes and >50 subtypes
  - Significant variation in nucleotide sequence
  - Propensity to mutate
  - Genotype 1 ~75% infections in the US
- **Approx 35000 new infections/ year**

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Hepatitis C – Scope of the problem

- Approximately 4 million infected in the US, most <50 yrs old
  - 3-4 x more common in African-Americans
- Transmission:
  - Most common IVDA (prior to 1990: blood transfusion)
  - Other: tattoo, hemodialysis, sexual contact, perinatal transmission, occupational
  - Unidentified source: 10%
- 10,000 deaths annually due to HCV related diseases
- Nearly half of cases of HCC in the US
  - Risk of developing HCC: 1-3%/ yr since development of cirrhosis

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Scope of the problem..

- 4 million Americans infected
- 85% develop chronic infection, of these 20% will develop cirrhosis
- Likelihood of developing cirrhosis:
  - Heavy alcohol intake
  - Age >40 yrs @ infection
  - Coinfection (HIV, HBV)
  - Male
  - African American
- HCV-cirrhosis most common indication for LTx (35-40%)

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HCV Treatment Terminology

- EVR (Early virologic response): ≥ 2-log decrease in HCV-RNA within 12 weeks of Rx
- ETVR (End of treatment response): Absence of HCV-RNA at completion of Rx
- SVR (Sustained virologic response): Persistent absence of HCV-RNA 6 months after the completion of Rx

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Natural History of HCV infection

- Acute hepatitis
- Chronic persistent hepatitis
- Cirrhosis
- Uncommon:
  - sponatneous resolution
  - Fulminant Hepatic Failure
  - Cholestatic hepatitis
- Extrahepatic manifestations

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Extrahepatic manifestations

- Autoimmune related:
  - Cryoglobulinemia
  - Renal failure
  - Porphyria
- Depression
- Diabetes?

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Cryoglobulinemia (CG)

- ~40% of HCV+ patients have asymptomatic cryoglobulinemia (without extrahepatic complications)
- CG syndrome: Proteinuria, neuropathy and arthritis
- CG ↑ the risk of cirrhosis by 4.9x
- CG assosicated with early recurrence and high severity
  - Hepatology 2002; 36: 978, Transplantation 2005;80: 448

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HCV and post-transplant diabetes

- Post-tx DM is more common in LT recipients who are HCV positive
- HCV + has the hazard ratio of 2.5 (vs HCV -)
- Onset of rec. HCV may coincide with DM in some patients
- Successful treatment of rec HCV helps with DM control
  - Transplantation. 2001;72:1066, Am J Surgery 2005; 189:552

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NIH Consensus Panels

- Panel meeting in 1997 (Hepatology 1997;26(Suppl 1):2S)
  - Transplantation was not even discussed!

Panel meeting in 2002 (Hepatology 2002; 36(Suppl. 1):s3)

- Qualitative HCV RNA assay with a lower limit of detection of 50 IU/mL or less (approximately 100 viral genes/mL): more sensitive, used to gauge termination of therapy
- Quantitative PCR (qPCR) or branched DNA (bDNA) signal amplification assay provides accurate information on HCV viral levels : used to gauge effectiveness of therapy
- Rx of rec-HCV after LT was considered experimental

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? Treatment in the acute hepatitis phase

- Prospective trial in Germany
  (N Engl J Med 2001;345:1452)
  - 44 patients
  - Treated with IFN-α2b for 24 weeks
  - ETVR 98%
- However, 30% patients may clear virus spontaneously (Dig Liver Dis 2003; 35(2):104)

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? Spontaneous resolution after acute infection

- Undetectable HCV RNA for > 6 mo
  - After acute infection ~50% of symptomatic patients, none of the asymptomatic patients (**Gastroenterology. 2003 Jul;125(1):80**)
  - Withdrawal of immunosuppression in KTx **(Gastroenterology 2003; 124: 1946)**

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Why treat?

- Risk of chronicity 80%
- Of chronic hepatitis patients: 20% develop cirrhosis over 20-30 years
- Of cirrhotic patients:
  - 30% risk of decompensation
  - 1-2%/yr risk of HCC

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Treatment of chronic HCV

- Guidelines for treatment of HCV infection in non-transplant population (Am J Med 2005;118: 808)
- Recommended Rx for patients w high risk of cirrhosis
  - Genotype 1
  - High HCV-RNA titer
  - Liver biopsy: early fibrosis w inflammation
  - All patients with chronic hepatitis
  - Continue Rx only if at-least 2 log ↓in HCV-RNA @ 12 wks (EVR)

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Treatment of chronic HCV…

- Early treatment regimenS (mid 90s): IFN monotherapy: SVR 10-12%
- Late 90s: IFN (2-3 inj/wk) + po Ribavirin: SVR 30%
- Current:
  - PEG-IFN α-2a 180 mg/wk + Ribavirin 1000mg/d (≤ 75kg) or 1200mg/d (> 75kg)
  - Monthly cost ~$2500

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Complications of Therapy

- IFN:
  - Depression
  - Exacerbation of autoimmune diseases/ transplant rejection
  - Flu like syndrome
- Ribavirin:
  - Hemolytic anemia (↑ incidence w renal dysfn)
  - Teratogenicity (even in males): contraception mandatory during and 6mo post-Rx

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Special considerations in LT recipients with HCV

- Pre-transplant: Treatment on the waiting list
- Transplant: Donor age, LDLT vs. DDLT
- Post-transplant:
  - Treatment: modality, timing, complications
  - Effect of immunosuppression
  - Histopathology: ACR vs. rec HCV
  - ? Retransplant

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HCV prevalence among LT Surgeons

- Anonymous survey in the annual ILTS meeting in Barcelona, 2003 (Hepatology. 2004;40:249A):
  - 117 LT surgeons responded
  - Prevalence was 0.8%
  - Prevalence of HCV in their patient population was 31-40%

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? Pre-transplant treatment of HCV

- Rationale: 30% higher graft loss if HCV-RNA titer high @ transplant (Hepatology 1998;28:823)
  - NIDDK database prospective analysis
  - 1990-1994, 675 patients (166 HCV +), 3 centers
  - HCV-RNA titer of $\geq 1x10^6$ vEq/mL 5-year survival 57% versus 84% for $< 1x10^6$ vEq/mL
  - Concern with highly variable techniques, population demographics and IS amongst the participating centers
- SVR may be achieved in 30%, of these 2/3rd remain virus free post-tx (J Hepatology 2003;39: 389)

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? Pre-transplant treatment…

- Liver Transpl 2002;8:350: Prospective randomized trial
  - 5 centers, 15 patients, 3 treatment arms (IFN a2B +/- Ribavirin), high CPT score ~11
  - ETVR 33%
  - Significant adverse events, incldg fatal
  - Discontinued
- Liver Transpl 2003;9:S90: Low accelerating dosage regimen (LADR)
  - CPT score ~7, 96 patients, Rebetron Rx
  - ETVR 42%, SVR in 22% - mostly in HCV-non 1 genotype
  - Pt w SVR remained virus free post LT
- **Final word:**
  - questionable benefit, may be used in Child's A or B cirrhotic (CPT 7 or MELD 18)
  - Data needed for PEG-IFN regimens

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Living Donor LT (LDLT) vs. Deceased Donor (DDLT) in HCV controversy

- **Controversy initiated by 2 abstracts at ATC-2002**
  - Rapid and early HCV recurrence following adult living donor liver transplantation [Abstract]. Am J Transpl 2002;2:63.
  - Hepatitis C recurrence in living donor liver transplantation [Abstract]. Am J Transpl 2002;2:138.
- Reportedly early and severe recurrence may be due to
  - Better HLA matching in LDLT (facilitating HLA restricted responses) (Transplantation 1995;59:640–642.)
  - Actively dividing (regenerating) liver may promote more replication (Liver Transpl 2003;9:S35)
- ↑ risk of severe rec. in LDLT (Hepatology 2004; 40:699)
- Increased risk of cholestatic HCV recurrence (Liver Transpl 2003;9:1028)

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LDLT controversy…

- More recent reports contradict increased risk of HCV recurrence in LDLT recipients (Am J Transpl 2005;5:149)
- SRTR data analysis reported similar survival for LDLT vs DDLT (LiverTranspl 2004;10:340)
- significantly lower fibrosis score @ 36 mo when compared with DDLT (Liver Transpl 2004; 10:1248)
- Similar survival, rate & severity of recurrence between LDLT and DDLT (Transplantation 2004; 77:1066)
- **Final Word: LDLT and DDLT have similar outcomes in HCV infected recipients**

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Donor Age and HCV recipient

- Increased risk of graft loss/ death @ 1yr for donor >50yr SRTR data analysis of ~7000 LT recipients (*Transplantation* 2005;80: 145):
- Concerns w this analysis:
  - Retrospective, multicenter (highly variable IS regimens, techniques etc)
  - Other significant variables not available or ignored: (HCC, BMI, donor sex, warm isch time etc)
  - No demographic comparison between younger vs older donor groups
- *Transplantation* 2004; 77(1): 84: Demographically matched single center analysis showing ↑risk w older donors (concern: very high reTx rate in both HCV+ and - recips)
- Other similar retrospective analyses indicate higher graft loss w older donors: Heptology2002;36:202, Gut 2002;51:248 (4.5x faster fibrosis)
- **Not everyone agrees…** (Ann Surg 2001;234:384, *Liver Transpl 2003;9:1174)*

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Donor age and HCV…

SRTR data analysis (Liver Transpl 2005;11:750)

- HCV+ recipient w donors older than 60 years:
  - relative risks of death, graft loss, and death due to inf was 1.92, 2.21, 2.65
  - 4 x higher risk graft loss due to rec HCV
- **Final word…**
  - More studies favor ↑ graft loss & fibrosis in older donor livers
  - ?Liver brings its intrinsic age (HCV outcome is worse if infected at older age) (*Liver Transpl 2005;11:384)*

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Using HCV + donors for HCV+ recipients

- Am J Transplant 2003;3:1167
  - 59 recipients of HCV+ donors between 1990 and 2000 were matched with recipients of HCV-ve donor using pretransplant risk factors
  - Patient and graft survival at 1 and 3 years was similar
  - HCV recurrence free survival at 1 and 3 years was similar
  - ALT and bilirubin levels were similar
- **Final word**: retrospective data, but appears safe to use in selected patients

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Recurrent HCV post LT

- Universal recurrence
- Hepatology 2000;32:1125
  - Viral titers are low immediately post-tx but then significantly increase, peak @ 4 mo.
  - Post-tx titers 10-100x higher than pre-tx
  - 4 mo titer may indicate future histological activity
- **3 Patterns of recurrence**:(J Hepatol 2005;42:448, Liver Transpl 2005;11:479)
  - Acute hepatitis
  - Chronic Hepatitis: more accelerated progression when compared to chr. Hepatitis in non-Tx population, cirrhosis in 25% @ 5 yr
  - Fibrosing Cholestatic Hepatitis: graft failure within 6 months
    - Associated w very high immunosuppression (OKT3, steroid pulse)
    - Very high HCV-RNA titers
    - ALT >500 U, GGT >1000 U, bilirubin >6 mg
    - Scant inflammation
    - Central hepatocyte ballooining

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↑Progression of fibrosis in recurrent HCV

- Older donor age
- High HCV-RNA titer pre-transplant
- OKT3 therapy
- Steroid boluses for ACR
- Genotype 1b
  - (Hepatology 2003;38:34, Transplantation 2004;77:226)

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What dictates the course of recurrent HCV?

- Forum on Liver Transplantation. J Hepatol 2005;42: 448
- High viral load (@ tx > 1meq/mL, >10meq/mL @ 4 mo)
- Genotype 1B
- Donor age >50 yrs
- Early histological recurrence (within 6 mo)
- Immunosuppression:
  - Net immunosuppression high
  - Abrupt change in Immunosuppression

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Post-transplant therapy of HCV

- **Pre-emptive Therapy (early post-tx):**
  - Rationale: low HCV RNA titers likely to be more susceptible
  - Poorly tolerated due to other problems:
    - Leucopenia, renal failure
    - Low SVR due to often required dose reductions
  - No difference in histological outcome when compared with Rx of established rec HCV
- **Treatment of established rec HCV:**
  - IFN or Ribavirin monoRx not very effective
  - PEG-IFN+Ribavirin protocols: (Transplantation 2004;77:190. J Hepatol 2004;40:669)
    - Not tolerated by ~40%
    - 26-45% SVR, including histological response in some
    - Genotype 1 less likely to be susceptible

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? Hepatitis-C Ig (HCIG) for recurrent HCV

- **Rationale:** French study showing ↓ HCV-RNA and hepatitis in LT recipients prior to 1990 who had received HBIG (Ann Intern Med. 1998;128:810)
- No beneficial effect of HCIG seen in another pilot study (J Hepatol 2002;36(Suppl 1):32)
- Recent RCT:(Liver Transpl 2005;11:941). 4 transplant centers, 18 patients randomized to low dose, high dose or control
  - Problem: Flu like symptoms, short ½ life of antibody
  - High dose patients had normalization of ALT
  - No effect on HCV-RNA
- **Final Word**: Innovative, but questionable. Need more patients, longer f/u and long-term effect on histology

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The effect of immunosuppression

- Many studies, often conflicting findings
- Worse recurrence and survival in recent era of LTx (since 2000) may be due to change in IS strategy
- Most agree: Overall immunosuppression does seem to have an impact on HCV recurrence and severity (Nature 2005; 436:973)
  - OKT3
  - High dose pulse steroids
- Not everyone agrees on:
  - MMF vs Aza
  - CsA vs Tacrolimus
- Prolonged maintenance immunosuppression may even retard fibrosis progression

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Immunosuppression…

- *Transplantation Proceedings 2005;* 37:1703
  - No difference between CsA vs Tac.
  - Less fibrosis with higher mean steroids (7.7mg/d v 3.3mg/d)
  - Bette outcome w Aza
- protective effect of steroids and Aza (Liver Transpl 2005;11:386, Hepatology 2003;38:34)
- Prolonged Aza and Steroid may be the reason for better outcome in earlier era
- Normal maintenance IS may protect against fibrosis progression *Transplantation Proceedings 2004;* 36: 3065
- ↑ graft loss due to rec. HCV when steroid pulse was used (*Transplantation Proceedings 2005;*37:1700)
- Steroid avoidance may be beneficial (Hepatology 2002;35:680)
- Rapid change in IS may be harmful (Nature 2005;436:073, Liver Transpl 2003;11:s63)

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Immunosuppresion…MMF and recurrent HCV

- SRTR data analysis of 11,670 LT recipients (1995-2001) comparing Tac+MMF+steroid vs Tac+steroid (Liver Transpl 2005;11:750). Patients in MMF arm
  - Better 4 yr graft survival
  - Less ACR
  - Less HCV recurrence leading to graft loss/death
  - Serum Creatinine: no difference
  - MMF did not make difference in CsA group (no explanation given)
  - No comparison presented between CsA vs Tac
- Another study showed worse outcome w MMF (Hepatology. 2003 Jul;38(1):34)

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The histopath conundrum…

- **Final word:**
  - No infallible clinical or histopathological marker
  - Suspect ACR if significant "ductitis" + portal endothelits + Eosinophils
  - Suspect rec HCV if sinusoidal dilatation + lymphoid aggregrates
  - HCV-RNA in liver biopsy specimen >10,000 copies/ mg tissue DNA
  - Remember rec HCV and ACR may co-exist

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? Re-transplantation for recurrent HCV

- Scope of the problem (Liver Transpl 2003;9:S73): ~45% of recent LT recipients are HCV+,
  - ~50% have clinical recurrence within one year
  - Recently transplanted patients have more rapid fibrosis (Hepatology 2002;36:202)
  - 20%-30% will develop cirrhosis in 5 yrs
  - 42% of rec. HCV cirrhosis pt will decompensate within 1 yr (J Hepatol 2000;32:673)

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Retransplantation…

- Patients undergoing reTx for rec. HCV do significantly worse
  - 27% of reTx (1997-2002) in SRTR for HCV (Liver Transpl 2005;11:434)
    - HCV pt had 30% higher mortality risk
  - 43% vs 74% (for non HCV reTx) 1 yr survival (Liver Transpl 2000;6:174)
- Predictors of worse outcome following reTx (ILTS consensus conference, Liver Transpl 2003;11:s1)
  - bilirubin> 10mg/dL
  - Creatinine >2.0mg/dL
  - Age>55 yr
  - Early recurrence w cirrhosis within 1 yr
  - Donor age >40 yrs
- ReTx not advised in Fibrosing Cholestatic Hepatitis type recurrence

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Antiviral Rx before re-Tx

- Poorly tolerated
- SVR achieved in <20%
- On the positive side, patients with SVR may have comparable survival to non-HCV patients after reTx

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Future directions/needs

- Better treatment regimens
  - Prevent fibrosis and HCC
  - Current strategies have significant adverse effects, poor tolerability and inadequate response
- Better designed trials instead of small sporadic studies that leave conflicting trails
- Better diagnostic accuracy in rec HCV vs ACR
- Unfortunately, with HCV and LT: worse is yet to come…
  - (HCV cirrhosis incidence will double by 2020 and infection prevalence will peak 2040)
    - Liver Transpl 2003;9:331

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