Hepatitis C and Kidney Transplantation

Simin Goral, MD
University of Pennsylvania Medical Center
Philadelphia, Pennsylvania
Hepatitis C Virus

- Small single stranded RNA virus
- Infection with HCV affects approximately 180 million people globally
- The prevalence is estimated to be approximately 2.4% worldwide with high geographic variability, ranging from <0.5% in Northern Europe up to 15% in Egypt
- Leading cause of chronic hepatitis, cirrhosis, and liver cancer
- At least 6 major genotypes - genotype 1 is the most common in North America, South America and Europe

Rosen H. NEJM 2011
Hepatitis C Infection

- The prevalence of HCV infection among HD patients in the US: average 9.3%, range: 6%-38% among dialysis centers; in Northern Europe is below 5%, and around 10% in most of southern Europe (Fabrizi F. ISRN Nephrol 2012)

- Among the kidney transplant population, the prevalence of anti-HCV positivity: 5%-46%, depending on the countries and/or centers

- The most important risk factors for HCV in dialysis patients: **blood transfusions and total time spent on dialysis**
Variation in hepatitis C virus (HCV) prevalence by patient’s time with end-stage renal disease (ESRD). The mean time on ESRD was 4.9 years, with a standard deviation of 5.4 years.

- Dialysis Outcomes and Practice Patterns Study (DOPPS)-prospective, observational study of HD patients randomly selected from 308 facilities in France, Germany, Italy, Japan, Spain, UK, and US; **Increased HCV prevalence-associated with longer time on dialysis, male gender, black race, diabetes, hepatitis B infection, prior renal transplant, and alcohol or substance abuse in the previous 12 months**

  *Fissell RB, et al. Kidney Int 2004*
Hepatitis C Infection-Dialysis

- Mortality rates are higher among HCV-infected dialysis patients than among HCV-negative patients
  - HCV infection is an independent predictor of death in dialysis patients, increasing the risk for death 1.62-to 2.39-fold
- Cirrhosis and other liver-related deaths are reported more frequently in HCV-infected dialysis patients than in those without the HCV

Nakayama E et al. JASN 2000
Kalantar-Zadeh K et al. JASN 2007
Hepatitis C-Transplant

• Improved long-term survival of HCV+ patients after kidney transplantation compared to patients on the waiting list.

• Long-term patient and graft survival rates are lower in HCV+ patients than in HCV- recipients.

• After transplantation, liver disease is more frequent in HCV+ patients than in HCV- patients.

• HCV+ patients have a higher risk for developing proteinuria, diabetes and infections after transplantation.

Transplant and Survival

• Single center data: UPenn experience
• 315 patients evaluated over a 10yr period
• Survival was better among transplanted patients

Hepatitis C and Survival After Kidney Transplantation

- A systematic review of the published medical literature concerning the impact of HCV infection on all-cause mortality and graft loss after transplantation
- 18 observational studies involving 133,530 unique renal transplant recipients

- Adjusted RR risk of all-cause mortality was 1.85

*Fabrizi F, et al. J Viral Hepat 2014*
- Adjusted RR of all-cause graft loss was 1.76

*Fabrizi F, et al. J Viral Hepat 2014*
Hepatitis C and Survival After Kidney Transplantation

• Meta-regression showed that living donor had a favorable influence on patient (p=0.031) and graft survival (p=0.01), whilst diabetes having a detrimental role on patient survival (P = 0.001)

• HCV-positive patients have an increased risk of mortality and graft loss after transplantation

Hepatitis C-Survival

- OPTN and SRTR database/Social Security Death Master File
- 75,629 HCV negative, and 3,708 HCV positive patients-kidney transplant 1995-2004
- Increased mortality risk for HCV-positive vs HCV-negative recipients, particularly among younger age groups
- The use of induction therapy was not associated with an increased mortality risk

Adjusted hazard ratio for HCV-positive serology of kidney recipients, by age at the time of transplantation, compared with HCV-negative recipients (reference=1.0); the age by HCV interaction was significant (P<0.0001).

Choice of Maintenance Immunosuppression on Mortality

- Choice of CNI - neutral
- Steroid use/avoidance - neutral
- MMF containing regimens were protective (HR 0.77)

<table>
<thead>
<tr>
<th>Medication</th>
<th>HR (use vs. no use)</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tacrolimus</td>
<td>1.03</td>
<td>0.79–1.35</td>
<td>0.83</td>
</tr>
<tr>
<td>Cyclosporin A</td>
<td>1.12</td>
<td>0.88–1.44</td>
<td>0.37</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>0.77</td>
<td>0.64–0.92</td>
<td>0.005</td>
</tr>
<tr>
<td>Sirolimus/everolimus</td>
<td>1.13</td>
<td>0.83–1.55</td>
<td>0.43</td>
</tr>
<tr>
<td>Steroid</td>
<td>1.16</td>
<td>0.79–1.71</td>
<td>0.44</td>
</tr>
</tbody>
</table>

The Presence of HCV

- Adverse effects on posttransplant morbidity and mortality
- The presence of HCV in ALL potential kidney transplant patients MUST be established during the evaluation process
- Inform and counsel patients in advance
- Try to improve the outcomes
Evaluation-HCV Infection

- Evaluation of patients with chronic HCV infection is warranted to determine stage of the disease and the need for HCV therapy
  - Decrease the risk for progression of HCV-associated liver disease
  - Stabilize kidney function in patients with HCV-related kidney disease
  - Prevent development of HCV-associated kidney disease after transplantation
- The “serological window” between acute infection and the detection of specific antibodies: average of 8 weeks, and in immunocompromised patients, may be delayed or absent.
Hepatitis C Testing

• Antibody detection via enzyme immunoassay (EIA)-used for screening
  • Detects antibody to core and nonstructural proteins
  • 3rd generation EIA 95% sensitivity, 88-95% PPV

• Issues:
  • False-negative results
  • Persistence of HCV antibodies in some patients who spontaneously clear the virus
  • Immunocompromised hosts may not have an antibody response even when infected with HCV; can not distinguish active infection
Hepatitis C Testing

• Nucleic acid testing (NAT)
  – Preferred especially in high prevalence areas
  – Based on RNA detection
  – Better for immunocompromised patients
  – Active infection vs persistent antibodies
Testing for HCV

• Patients on hemodialysis should be tested when they first start HD or when they transfer from another HD facility
  • In HD units with a low prevalence of HCV, initial testing with EIA (and, if positive, followed by NAT) should be considered
  • In HD units with a high prevalence of HCV, initial testing with NAT should be considered

KDIGO Guidelines, Kidney Int 2008
Figure 1. Algorithm for screening for HCV in patients on hemodialysis. EIA, enzyme-linked immunoassays; HCV, hepatitis C virus; NAT, nucleic acid amplification test; RIBA, recombinant immunoblot assay.
KDIGO guidelines strongly recommend:

- All kidney transplant candidates should be screened for HCV infection
- Serology, hep c viral load, and genotyping
Role of Pretransplant Liver Biopsy

- Noninvasive measures (liver enzymes and viral load) correlate poorly with disease activity and fibrosis
  - 22% of patients with ESRD had normal liver function tests despite of severe bridging fibrosis and/or cirrhosis (Sterling RK, et al. Am J Gastroenterology 1999)
- Liver biopsy - remains the “imperfect gold standard” - also recommended by KDIGO
Assessing the histologic lesions in chronic hepatitis C using two separate scores, one for necroinflammatory grade (A for activity) and another for the stage of fibrosis (F).
Pretransplant Liver Biopsy

- KDIGO: Liver biopsy for all viremic patients
- Measurement of hepatic venous pressure gradient (HVPG)
  - Provides important prognostic information in patients with compensated liver cirrhosis: HVPG ≥ 10 mmHg - clinically significant portal hypertension
Cirrhosis is not an absolute contraindication for transplantation

Liver disease may progress while on dialysis - patients might need repeat liver biopsies

- 110 HCV+ patients; 13 stayed on waiting list
- Of those with >1 pretransplant liver biopsy, 62% had interval progression of liver disease while on the waiting list (Roth D, et al. J Am Soc Nephrol 2011)
Pretransplant Management

- Re-biopsy every 5 years with mild/moderate fibrosis in the baseline biopsy and every 3 years with advanced fibrosis - KDIGO
- At least a yearly evaluation (sonography, lab tests) should be done in patients with no cirrhosis
- In patients with cirrhosis awaiting transplantation:
  - Ultrasound should be performed at least every 6 months (with or without alfa-fetoprotein measurement) to exclude HCC
  - The surveillance of esophageal varices also should be done regularly by endoscopy, according to international guidelines

Patients with Advanced Liver Disease

-1- and 3-year patient survival rates: 88.9% and 88.9% vs 96.3% and 77.9% for groups C and NC, respectively (P=0.76). 1- and 3-year graft survival rates were 75% and 75% vs 92.1% and 75.1% for groups C and NC, respectively (P=0.72).

- In a compensated HCV+ patient with cirrhosis and ESRD with HPVG<10 mm Hg, combined liver-kidney transplant may be unnecessary; kidney transplant alone may be performed safely.

Use of HCV-positive Kidneys

- HCV Ab+ recipients who are viremic can accept HCV+ kidneys
- Rationale: could shorten waiting times and increase organ utility
- Problem: risk of superinfection
- Only 49% of centers in the US will transplant HCV+ donor kidneys
- Usually limited to recipients who are viremic with known genotype 1
Transplanting HCV-positive Kidneys

- 162 HCV+ recipients received a kidney from HCV+ donor (group 1) and 306 from HCV- donor (group 2)
- Mean follow-up: 74.5 months
- Five-and 10-year patient survival similar: 84.8% and 72.7% in group 1 vs. 86.6% and 76.5% in group 2 (p = 0.250)

Morales JM et al. Am J Transplant 2010
HCV+ Donors

- A trend toward lower graft survival in HCVR+ transplanted with kidneys from HCVD+
  - Might be due to the higher frequency of pretransplant HCV RNA positive and higher frequency of chronic allograft nephropathy
- No differences in the incidence of decompensated liver disease between the groups—though no routine biopsies

Morales JM et al. Am J Transplant 2010
Posttransplant Interferon

• The use of interferon in the posttransplant setting-associated with an increased risk of allograft rejection (40-100%)

• Responses to antiviral therapy are poor; 14% achieve sustained virological response; tolerance is poor

• KDIGO recommends reserving posttransplant treatment with IFN based regimens only for patients with fibrosing cholestatic hepatitis or in those with de novo cryoglobulinemic GN within the allograft

Rostaing L et al. Contrib Nephrol 2012
Posttransplant Complications in Patients with HCV

- Higher risk for developing proteinuria, chronic allograft dysfunction, and glomerulonephritis
- New-onset diabetes after transplantation (NODAT)
- Cardiovascular diseases
- Infections and posttransplant lymphoproliferative disease
- Progression of liver disease
HCV-Kidney Disease

- HCV is a cause of both native and transplant GN
- Can be recurrent GN, *de novo* GN or transplant glomerulopathy
- Kidney biopsy-diagnostic: 44 (45.8%) HCV+ and 52 from HCV- recipients

<table>
<thead>
<tr>
<th></th>
<th>HCV+</th>
<th>HCV-</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>De novo MPGN</strong></td>
<td>45.4%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>De novo MN</strong></td>
<td>18.2%</td>
<td>7.7%</td>
</tr>
<tr>
<td><strong>TGP</strong></td>
<td>11.4%</td>
<td>11.5%</td>
</tr>
<tr>
<td><strong>Recurrent</strong></td>
<td>4.5%</td>
<td>15.5%</td>
</tr>
<tr>
<td><strong>CAN</strong></td>
<td>20.5%</td>
<td>59.6%</td>
</tr>
</tbody>
</table>

*Cruzado JM, et al. Am J Transplant 2001*
• *de novo* GN, especially type 1 MPGN, was associated with a very poor graft outcome in HCV+ patients
• Multivariate analysis: HCV+ serology was the only independent predictor of graft loss
• During the follow-up, 77.3% HCV+ and 42.3% HCV- cases developed ESRD and returned to dialysis (p = 0.001)

*Cruzado JM, et al. Am J Transplant 2001*
Screening for Kidney Disease Posttransplant - KDIGO and ERBP Work Group

- Urinalysis: in all stable HCV+ recipients every 3-6 months in the first posttransplant year; then at least annually
- Patients with new onset proteinuria (either UPCR>1 or 24-h urine protein >1 g on two or more occasions) - biopsy with IF and EM
- RAS blockade is the preferred treatment
- New antivirals?
New Onset Diabetes After Transplantation (NODAT)

- NODAT is an important complication after kidney transplantation
- The incidence increases with time after transplant
- 25% of all recipients have diabetes by 3 years posttransplant
- USRDS study identified risk factors for NODAT
  - Advanced age, non-caucasian, tacrolimus use, and HCV infection

NODAT-Mechanism

- 20 HCV+ and 22 HCV- kidney recipients, 14 HCV+ nontransplant patients and 24 HCV- nontransplant (healthy) subjects
- A 3-h IV glucose tolerance test
- Also peripheral insulin sensitivity; pancreatic insulin secretion, hepatic insulin uptake, pancreatic antibodies and proinflammatory cytokines in serum (tumor necrosis factor-, interleukin-6, high-sensitive C-reactive protein)

• Significant decrease of insulin sensitivity in both HCV+ groups (with and without transplantation) compared to HCV-groups
• No significant differences in insulin secretion and hepatic insulin uptake between groups
• The presence of HCV infection was independently associated with impaired insulin sensitivity (p = 0.008)/ increased peripheral insulin resistance in transplant recipients

NODAT Management

- KDIGO recommends:
  - Screening HCV+ recipients pretransplant with an OGTT to identify those with diabetes
  - Following fasting glucose levels weekly for the first 3 months posttransplant
  - Referring patients who meet ADA criteria for diabetes (2 fasting glucose > 125mg/dl) to an endocrinologist
Infections-HCV

- RESITRA/REIPI-prospective cohort study to delineate incidence and etiology of posttransplant infection: 1302 patients, 8% HCV+

**TABLE 3. Type of infectious syndrome and causative agent according to anti-HCV status**

<table>
<thead>
<tr>
<th>Variables, n (%)</th>
<th>Anti-HCV-positive recipients (n=105)</th>
<th>Anti-HCV-negative recipients (n=1197)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious syndrome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any infection</td>
<td>48 (45.7%)</td>
<td>481 (40.2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Overall incidence rate *</td>
<td>0.82</td>
<td>0.74</td>
<td>NS</td>
</tr>
<tr>
<td>Bacterial infection</td>
<td>42 (40.0%)</td>
<td>394 (32.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cystitis</td>
<td>18 (17.1%)</td>
<td>238 (19.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Upper urinary tract infection c</td>
<td>13 (12.4%)</td>
<td>82 (6.9%)</td>
<td>0.037</td>
</tr>
<tr>
<td>Bloodstream infection</td>
<td>9 (8.6%)</td>
<td>42 (3.5%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>3 (2.9%)</td>
<td>48 (4.0%)</td>
<td>NS</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>6 (5.7%)</td>
<td>45 (3.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Intraabdominal infection</td>
<td>3 (2.9%)</td>
<td>18 (1.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.0%)</td>
<td>22 (1.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>CMV infection</td>
<td>10 (9.5%)</td>
<td>125 (10.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Asymptomatic infection</td>
<td>4 (3.8%)</td>
<td>49 (4.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Viral syndrome</td>
<td>3 (2.9%)</td>
<td>42 (3.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>End-organ disease</td>
<td>1 (1.0%)</td>
<td>9 (0.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Viral infection (other than CMV)</td>
<td>2 (1.9%)</td>
<td>69 (5.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>2 (1.9%)</td>
<td>25 (2.1%)</td>
<td>NS</td>
</tr>
<tr>
<td>Invasive fungal infection</td>
<td>1 (1.0%)</td>
<td>14 (1.2%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Infections-HCV

- HCV infection induces a state of immunodeficiency after solid organ transplantation:
  - A decrease in the rate of naive T-helper lymphocytes and the T-cell mitogen proliferative response
  - A severe disturbance of B-cell homeostasis

Micheloud D, et al. Transplant Infect Dis 2009
New Developments

- Transient elastography (FibroScan, Echosens): a novel noninvasive technique measures liver stiffness by assessing the velocity of a shear wave created by a transitory vibration
- Thresholds for a high likelihood of clinically significant fibrosis (Metavir score ≥2) have been defined
- Has an increased failure rate among obese patients
- It has not been approved by the FDA
New Developments

• FibroSure:
  • Biomarker test that uses the results of six blood tests to generate a score that is correlated with the degree of liver damage/fibrosis in people with a variety of liver diseases
  • Alpha-2-macroglobulin, Haptoglobin, Apolipoprotein A1, Gamma-glutamyl transpeptidase (GGT), Total bilirubin, and Alanine transaminase (ALT)
New Developments

- Fibrotest (FT) and liver stiffness measurement (LSM) for assessing liver fibrosis in kidney transplant patients with chronic HBV or HCV infection
- 38 consecutive kidney transplant patients with HCV (n = 26) or HBV (n = 12) underwent liver biopsies followed by a FT and LSM
- Diagnosis of patients with severe liver fibrosis (F3/F4) by FT and LSM differed by 38.4% from the liver biopsy data
- The FT and LSM are acceptably accurate for diagnosing mild liver fibrosis in kidney transplant patients with chronic HCV or HBV infections, but their diagnostic value for predicting severe liver disease needs to be confirmed

New Antivirals

• Protease inhibitors: telaprevir or boceprevir-increase response rate to 80%

• Nucleotide polymerase inhibitors
  • Use of sofosbuvir and ribavirin resulted in a rapid decline in circulating HCV RNA levels, with similar reductions in the two studies and among patients with HCV genotype 2 or 3 infection (up 99% response rate) (Jacobson IM, et al. NEJM 2013)

• Close monitoring of CNI levels while on treatment should be performed
Future Studies

- Further studies using protease/polymerase inhibitors are needed in certain subgroups of patients
  - Patients with lower response rates, including black patients
  - Patients without a response to prior treatment
  - Liver and kidney transplant recipients
  - Patients coinfected with HIV
  - Patients with high baseline viral load, advanced fibrosis, or insulin resistance
Summary

• All kidney transplant candidates should be screened for HCV, preferably with NAT.
• Liver biopsy in viremic patients for now—can this be replaced by FibroSure and Fibroscan?
• HCV therapy should be offered pretransplant to all; with the use of new antivirals most likely posttransplant as well.
• Although patient and allograft outcomes are inferior to HCV negative recipients survival is better than on dialysis.
• HCV+ kidneys are a reasonable option for viremic patients to shorten waiting times.