Hepatitis C and renal disease: An overview

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Disclosure of Financial Relationships

No Disclosures
Hepatitis C and renal disease

- Basic HCV virology and epidemiology
- Impact of HCV on patients with ESRD
- Role of hepatoma screening
- HCV associated renal disease
HCV: A primer
## Characteristics of Hepatitis A, B and C

<table>
<thead>
<tr>
<th></th>
<th>Hepatitis A</th>
<th>Hepatitis B</th>
<th>Hepatitis C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of acute inf. in the US/yr</td>
<td>179,000</td>
<td>185,000</td>
<td>38,000</td>
</tr>
<tr>
<td>No of chronic infected persons</td>
<td>-</td>
<td>1,250,000</td>
<td>2,700,000</td>
</tr>
<tr>
<td>No of chronic infected persons in the world</td>
<td>-</td>
<td>350 Million</td>
<td>170 Million</td>
</tr>
<tr>
<td>Treatment</td>
<td>None</td>
<td>IFN alpha, lamivudine, adefovir</td>
<td>IFN alpha+RBV</td>
</tr>
<tr>
<td>Prophylaxis</td>
<td>Vaccine, immune globulin post exposure</td>
<td>Vaccine, Hep B immune globulin post exposure</td>
<td>None</td>
</tr>
</tbody>
</table>

Lauer GM, Walker BD, NEJM 2001
Hepatitis C Virus Infection: United States

- New infections (cases)/year 1985-89 242,000
- 1997 38,000

- Deaths from acute liver failure Rare

- Persons ever infected (1.8%) 3.9 million (3.1-4.8)*

- Persons with chronic infection 2.7 million (2.4-3.0)*

- HCV-related chronic liver disease 40% - 60%

- Deaths from chronic disease/year 8,000 - 10,000

- Liver Transplants**
  - Number ~2,000/year

*95% Confidence Interval
**UNOS, 1999
Source: CDC/Hepatitis Branch
HCV Infection

Genotype Distribution

Prevalence of HCV Infection, United States, 1990

**HCV Infection**

### Groups at Increased Risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Average Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persons who have ever injected illegal drugs</td>
<td>~80%</td>
</tr>
<tr>
<td>Clotting factor recipients (before 1987)</td>
<td>~85%</td>
</tr>
<tr>
<td>Transfusion or solid-organ recipients (&lt;July 1992)</td>
<td>~5%</td>
</tr>
<tr>
<td>Long-term hemodialysis patients</td>
<td>~10%</td>
</tr>
<tr>
<td>Persons with high-risk sexual behavior</td>
<td>~5%</td>
</tr>
<tr>
<td>Incarcerated</td>
<td>~30%</td>
</tr>
</tbody>
</table>

Natural History of Hepatitis C Virus Infection in General Population

- **100 Acute HCV Infections**
  - 20% Recovery: 20 Patients
  - 80% Persistent Infection:
    - 30% Stable Chronic Hepatitis: 24 Patients
    - 40% Variable Progression: 32 Patients
    - 30% Severe Progressive Hepatitis: 24 Patients
    - Anti-Viral Therapy (56 Patients):
      - Treatment Failure 65%:
        - 36 Patients
      - Sustained Response 35%:
        - 20 Patients

Favorable Outcome: 64/100 = 64%
Severe Outcome: 36/100 = 36%

Courtesy Alter H, Seeff L. Sem Liver Disease, 2000
Risk Factors for Accelerated Progression to Fibrosis/Cirrhosis

- **Modifiable**
  - Alcohol consumption
  - Hepatic steatosis, insulin resistance
- **Non-modifiable**
  - Increased age at infection
  - Longer duration of infection
    - Mean time to cirrhosis is ~20-25 years
  - Male gender
- Co-infection with HIV (25% vs. 6.5% HCV alone) or HBV
- Viral load, HCV Genotype *not* associated with progression

HCV in patients with ESRD: Diagnostic testing
Diagnostic testing in HCV

- 3rd generation EIA
  - 95+ % sensitivity and specificity

- Transcription mediated assays
  - Able to detect HCV RNA down to <10 IU/mL
  - Typical viral load in ESRD patients in the 100,000 IU/mL range

- Genotyping typically successful when viral load > 1000 IU/mL
Diagnostic testing for HCV in MHD

Diagnostic testing for HCV in ESRD

Table 1. Comparison of the TMA and EIA Diagnostic Tests for HCV Infection

<table>
<thead>
<tr>
<th></th>
<th>TMA&lt;sup&gt;+&lt;/sup&gt;</th>
<th>TMA&lt;sup&gt;-&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIA&lt;sup&gt;+&lt;/sup&gt;</td>
<td>25 (8)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>EIA&lt;sup&gt;-&lt;/sup&gt;</td>
<td>22 (7)</td>
<td>263 (84)</td>
</tr>
<tr>
<td></td>
<td>47 (15)</td>
<td>267 (85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Specificity (%)</td>
<td></td>
<td>99</td>
</tr>
</tbody>
</table>

Kalantar-Zadeh K et al., Am J Kidney Dis 2005;46:290-300-UCLA
## Prevalence of HCV in RRT

<table>
<thead>
<tr>
<th>Country</th>
<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Netherlands</td>
<td></td>
<td>2.9-3.4%</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1.5%</td>
<td>5%</td>
</tr>
<tr>
<td>Germany</td>
<td>4.6%</td>
<td>7%</td>
</tr>
<tr>
<td>Spain</td>
<td>2.8%</td>
<td>19-30%</td>
</tr>
<tr>
<td>Italy</td>
<td>4.3%</td>
<td>47-60%</td>
</tr>
<tr>
<td>USA</td>
<td>2.4%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Brazil</td>
<td>12-45%</td>
<td>11-26%</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td></td>
<td>68%</td>
</tr>
<tr>
<td>Japan</td>
<td>2.1%</td>
<td>27%</td>
</tr>
</tbody>
</table>

Fehr T, Ambuhl PM. Nephrol Dial Transplant 2004;19:1049-1053
Testing for HCV in ESRD: KDIGO Recommendations

1.1.2 Testing for HCV should be performed in patients on MHD and kidney transplant candidates (Strong)

- CDC recommends EIA testing
- NKF-KDOQI recommends EIA in low prevalence centers/populations, NAT testing in high prevalence centers/populations
- Must take into account individual patient risk factors as well-?EIA for low risk patients, NAT for high risk patients

Testing for HCV in ESRD: KDIGO Recommendations

- 1.2.2 For patients on hemodialysis who test negative for HCV, retesting every 6-12 months with EIA should be considered (Moderate)
  - NKF-KDOQI concurs with role of EIA rather than more expensive NAT testing in conjunction with monthly LFTs
  - NKF-KDOQI: Optimal frequency of follow-up testing in US HD units requires further study
  - Consistent with CDC recommendations

1.2.3 Testing for HCV with NAT should be performed for hemodialysis patients with unexplained abnormal transaminase levels (Strong)
Testing for HCV in ESRD: KDIGO Recommendations

- 1.2.4 If a new HCV infection in a hemodialysis unit is suspected to be nosocomial, testing with NAT should be performed in all patients who may have been exposed (Strong)

- Repeat testing with NAT is suggested within 2-12 weeks in initially NAT-negative patients (Weak)

Clinical outcomes of HCV infection in ESRD
### Table 2. Histopathologic changes among hemodialysis and normal renal function patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group with ESRD ($n = 36$) $[\text{mean} \pm \text{SD (range) or n (%)}]$</th>
<th>Group with NRF ($n = 37$) $[\text{mean} \pm \text{SD (range) or n (%)}]$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis staging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>19 (52.8)</td>
<td>10 (27)</td>
<td>0.025$^a$</td>
</tr>
<tr>
<td>1</td>
<td>11 (30.6)</td>
<td>15 (40.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4 (11.1)</td>
<td>7 (19.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (5.5)</td>
<td>5 (13)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14 (39)</td>
<td>6 (16.2)</td>
<td>0.003$^a$</td>
</tr>
<tr>
<td>1</td>
<td>12 (33.3)</td>
<td>9 (24.3)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>10 (27.7)</td>
<td>15 (40.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0)</td>
<td>7 (19)</td>
<td></td>
</tr>
<tr>
<td>Steatosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>6 (16.3)</td>
<td>21 (56.8)</td>
<td>$&lt;0.001^a$</td>
</tr>
<tr>
<td>no</td>
<td>30 (83.3)</td>
<td>16 (43.2)</td>
<td></td>
</tr>
</tbody>
</table>

## Spectrum of liver disease in HCV positive dialysis patients

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of pts</th>
<th>Normal ALT</th>
<th>Bridging fibrosis</th>
<th>Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caramelo</td>
<td>33</td>
<td>21%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>Pol</td>
<td>17</td>
<td>69%</td>
<td>NR</td>
<td>12%</td>
</tr>
<tr>
<td>Sterling</td>
<td>50</td>
<td>96%</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Glicklich</td>
<td>22</td>
<td>59%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Martin</td>
<td>37</td>
<td></td>
<td>8%</td>
<td>24%</td>
</tr>
<tr>
<td>Cotler</td>
<td>46</td>
<td>74%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Roth</td>
<td>152</td>
<td></td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Liver biopsy in ESRD

- Only reliable method to determine histology
- Risks appear comparable to non-ESRD patients (~1% complication rate)
- Use of DDAVP controversial, and without significant data to support
  - We do not use it any longer
- We recommend non-heparin dialysis day after procedure
  - Others recommend no heparin day before and day after procedure (i.e. Penn)
  - Data to support either approach limited to anecdotes

Pawa S et al., Clin Gastro and Hepatol 2007;6:1316-1320
“Patients on chronic hemodialysis should be well dialyzed prior to liver biopsy and heparin should be avoided if at all possible” (Class I, Level C)

Transjugular biopsy in PD patients?
General care of the HCV infected renal patient

- Alcohol avoidance
- Vaccination for HAV and HBV when appropriate
- Avoidance of chronic marijuana usage
- Control of obesity/insulin resistance
  - ? If applicable in ESRD
- Consideration of hepatoma screening in patients with bridging fibrosis or cirrhosis
  - No data in ESRD
  - Practice guidelines recommend AFP and imaging q 6-12 months in patients with stage 3 or 4 fibrosis

HCV and renal disease
HCV associated rheumatologic diseases

- Cryoglobulinemia
- Sjogren’s syndrome
- Fibromyalgia
- Membranoproliferative GN
- Membranous GN
- Antiphospholipid antibody syndrome
- ?SLE
Autoantibodies in HCV

- ANA 10-30%
- ASMA 60-70%
- RF 60-80%
- Anticardiolipin Abs 22%
- Antithyroid Ab 42%

HCV and cryoglobulinemia

- Essential mixed cryoglobulinemia (type II)
  - Not essential anymore
  - >90% related to chronic HCV infection
- Cryoglobulins consist of:
  - Rheumatoid factor
  - IgG
  - HCV specific antibodies
  - HCV protein

Agnello V, Chung RT, Kaplan LM  NEJM 1995;327:1490-1495
HCV and cryoglobulinemia

- B cell mediated
  - thus may respond to rituximab

- Cryoglobulins present in up to 50% of unselected HCV patients
  - Typical cryocrit < 3%

- Symptomatic cryoglobulinemia occurs in ~1% of chronic HCV patients
  - Cryocrit tends to be higher

- Leukocytoclastic vasculitis, purpura, neuropathy, renal disease
HCV and MPGN

- HCV major cause of MPGN
- Associated with longstanding HCV
- Liver disease often mild or clinically not apparent
- Cryoglobulins present 50-70% of cases, but other systemic manifestations may be absent
- HCV Ab (ELISA) positive
- HCV RNA measurable
- Complement low
- RF positive

A membro-proliferative pattern, with intense mesangial proliferation and peripheral expansion associated with centrolobular sclerosis (lobular MPGN) is evident. Moderate endocapillary infiltration of mononuclear leukocytes also is present (Masson trichrome x 250).

Kidney International 1998;54:650-671
Immunofluorescence staining for C3 in MPGN
Therapy of HCV MPGN

- Treat the HCV!
- Published results poor
  - Bulk of published data used suboptimal pharmacologic therapy
  - Virtually no data on PEG-IFN/ribavirin
  - Results should parallel HCV outcomes and should be much better than older reports (more from Bob Brown in a few minutes)
- Need to be careful with ribavirin dosing in renal insufficiency
Summary

- HCV common in patients with ESRD and transplant recipients
- Diagnostic testing in MHD patients challenging and not optimally worked out
- Advanced HCV relatively uncommon in ESRD
- HCV an infrequent but recognized cause of renal disease
- Excess deaths in HCV renal transplants due to liver disease - DON’T IGNORE IT!
- Therapy of HCV in ESRD and post-transplant challenging but improving
Questions?