Co-infected health-care workers

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Co-infected health-care workers = HBV + HCV

HBV + HDV
HBV + HCV
Prevalence of co-infection

• HBV and HCV share several modes of transmission
• Co-infection by the two viruses is not uncommon.
  – In patients with chronic HBV infection: 10-20% anti-HCV +

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  - In patients with chronic HBV infection: 10-20% anti-HCV +

Selection bias: Hospital based patient groups

Co-infection associated with a more severe histological liver disease

- Fibrosis score: VHB&VHC > VHC, VHB&VHC > VHB
- Prevalence of cirrhosis: VHB&VHC > VHC, VHB&VHC > VHB
- Hepatocellular carcinoma: VHB&VHC > VHC, VHB&VHC > VHB
- Repeatedly elevated ALT: VHB&VHC > VHB

Sagnelli et al. Infection 2004
Zarski et al. J Hepatol 1998
Gaeta et al. J Hepatol 2003
Kirk et al. Hepatology 2004
Prevalence of co-infection

- HBV and HCV share several modes of transmission
- Co-infection by the two viruses is not uncommon.
  - HBsAg chronic carriers: 7% anti-HCV + (59/837)
    - 14 liver units throughout Italy
    - Patients routinely tested irrespective of the presentation modalities
    - 12 month period

Prevalence of co-infection

- HBV and HCV share several modes of transmission
- Co-infection by the two viruses is not uncommon.

- HBsAg positive or anti-HBs positive HCWs: 3.1% anti-HCV + (42/1357)
  - Five hospitals personnel, Latium region, Italy (n=5813)
  - HCWs’ pre-vaccination screening for HBsAg +

Impact of HBV on HCV
Impact of HBV on spontaneous HCV clearance

- **Objective**: factors associated with HCV clearance
- **Study population**:
  - 203 spontaneously HCV-recovered subjects (HCV Ab+/RNA-)
  - 293 chronically HCV-infected patients (HCV Ab+/RNA+)
- HIV co-infection negatively associated with HCV clearance (OR 0.37; 0.16-0.83)
- HBV co-infection positively associated with HCV clearance (OR 5.0; 1.26-28.6).

Piasecki et al. Hepatology 2004
Impact of HBV on spontaneous HCV clearance

Table 4. HBV and HIV Coinfections: Differences in the Seroprevalence of Markers for HBV and HIV Exposure in Recovered and Chronically HCV-Infected Male Veterans

<table>
<thead>
<tr>
<th>Serological Groups</th>
<th>Chronic (n = 293)</th>
<th>Recovered (n = 203)</th>
<th>Unadjusted OR</th>
<th>95% CI</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbsAg+</td>
<td>3/276 (1.1%)</td>
<td>10/192 (5.2%)</td>
<td>5.0</td>
<td>1.26-28.6</td>
<td>.008</td>
</tr>
<tr>
<td>HbcAb+ †</td>
<td>166/251 (66.1%)</td>
<td>117/168 (69.6%)</td>
<td>1.17</td>
<td>0.75-1.83</td>
<td>.452</td>
</tr>
<tr>
<td>HbsAb+</td>
<td>98/272 (36%)</td>
<td>74/184 (40.2%)</td>
<td>1.19</td>
<td>0.80-1.79</td>
<td>.365</td>
</tr>
<tr>
<td>HIV+ among those tested</td>
<td>39/153 (25.5%)</td>
<td>9/78 (11.5%)</td>
<td>0.38</td>
<td>0.15-0.87</td>
<td>.014</td>
</tr>
</tbody>
</table>

NOTE. Percentages are based on all available data. Numbers shown are those subjects for which data was available from the total for each group.
*Chi-square test for categorical variables.
†HbcAb positive also tested for HBsAb.
Impact of HBV on HCV replication

- Serum HCV RNA:
  - In 41%–65% anti-HCV + and HBsAg+
  - In 90%–98% anti-HCV +

Wang et al. J Gastroenterol 1999
Mathurin et al. J Viral Hepatol 2000
Sagnelli et al Hepatology 2000
Impact of HBV on HCV replication

• HCV-RNA levels lower in HBV&HCV co-infections than in HCV infection:

• HCV RNA level lower in HBV DNA positive than in HBV DNA negative patients

Jardi et al. Hepatology 2001
Chu et al. Scand J Gastroenterol 2004
Zarski et al. J Hepatol 1998
Impact of HBV on HCV replication

HBV-DNA viral load (copies/mL)

- < $10^3$
- $10^3$-$10^4$
- $10^4$-$10^5$
- $10^5$-$10^6$
- > $10^6$

Jardi et al. Hepatology 2001
Impact of HBV on HCV replication

HBV DNA replication inhibits HCV RNA replication in patients with chronic active HBV&HCV

Jardi et al. Hepatology 2001
Impact of HCV on HBV
Impact of HCV on HBV replication

1200 patients
anti-HCV +

1 051 (87.6%)
HCV RNA +

11 (1.0%)
HBsAg+

134 (11.1%)
HCV RNA -

16 (11.9%)
HBsAg+
Impact of HCV on HBV replication


<table>
<thead>
<tr>
<th>HCV RNA +</th>
<th>HBe Ab +</th>
<th>HBe Ag +</th>
<th>HCV RNA -</th>
<th>HBe Ab +</th>
<th>HBe Ag +</th>
</tr>
</thead>
</table>

Fig. 1. Serum HBV DNA levels (copies per ml) in patients with serum HCV RNA positivity and HBeAg seroconversion (group 1), in patients with serum HCV RNA positivity and without HBeAg seroconversion (group 2), in patients with serum HCV RNA negativity and HBeAg seroconversion (group 3), and in patients with serum HCV RNA negativity and without HBeAg seroconversion (group 4). *, P < 0.05 compared with group 2. **, P < 0.05 compared with group 4. ***, P < 0.005 compared with group 4.
Table 1  Comparison of demographic, clinicopathological and virological features of chronic hepatitis B patients with and without concurrent HCV and HBV infection

<table>
<thead>
<tr>
<th></th>
<th>Chronic hepatitis B</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HCV infection</td>
<td>HCV infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>positive N (%)</td>
<td>negative N (%)</td>
<td>P</td>
</tr>
<tr>
<td>Patients’ no.</td>
<td>18</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>12/6</td>
<td>67/15</td>
<td>NS</td>
</tr>
<tr>
<td>Age (year)*</td>
<td>42.8 ± 11.5</td>
<td>33.4 ± 10.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALT* (IU/L)</td>
<td>83.8 ± 25.9</td>
<td>200.3 ± 30.3</td>
<td>0.08</td>
</tr>
<tr>
<td>HBeAg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>2 (11%)</td>
<td>61 (74%)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>16 (89%)</td>
<td>11 (26%)</td>
<td></td>
</tr>
<tr>
<td>HBV DNA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>6 (33%)</td>
<td>65 (79%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Negative</td>
<td>12 (67%)</td>
<td>17 (21%)</td>
<td></td>
</tr>
<tr>
<td>HBV-DNA levels* (log Meq/mL)</td>
<td>6.00 ± 0.63</td>
<td>7.65 ± 0.38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Histopathology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic persistent hepatitis</td>
<td>4 (22%)</td>
<td>22 (27%)</td>
<td></td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>12 (67%)</td>
<td>51 (62%)</td>
<td></td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2 (11%)</td>
<td>9 (11%)</td>
<td></td>
</tr>
</tbody>
</table>

*The continuation variables were represented as mean ± standard deviation.
Impact of HCV on HBV replication
Dai et al. J Gastroenterol Hepatol 2001

Table 3  Stepwise logistic regression analysis of factors significantly associated with hepatitis B e antigen seroconversion in chronic hepatitis B virus carriers

<table>
<thead>
<tr>
<th>Factors</th>
<th>Comparison</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Per year increase</td>
<td>0.932 (0.886–0.980)</td>
</tr>
<tr>
<td>Concurrent HCV</td>
<td>Positive versus</td>
<td>0.057 (0.012–0.298)</td>
</tr>
<tr>
<td>and HBV infection</td>
<td>negative</td>
<td></td>
</tr>
</tbody>
</table>
HCV-core protein can bind to HBV-RNA and suppress HBV gene expression and replication.

HBV replication would be more effectively inhibited by HCV genotypes 1 and 3 than the remaining HCV genotypes (HBV core protein and the 101-102 core domain of HCV genotypes 1 and 3 share an important Arg-rich motif).

Pontisso et al. Antiviral Therap 1998
Interplay of HBV and HCV in cases of combined infection:

Decreased replication level (or suppressed activity) of one or both viruses: decreased risk of transmission?
Risk factors for HCV transmission after occupational exposure in health care workers (HCWs): a European case-control study (ANRS)


GERES, Paris, France ; Istituto Nazionale per le Malattie Infettive, Rome, Italy ; InVS, Saint-Maurice , France ; Hospital Vall d'Hebron, Barcelona, Spain; Div.Infect Dis and Hospital Epidemiol, Zurich, Switzerland; HIV & STI Div CDSC, London, UK

Yazdanpanah ICAAC 2003
**Impact of source patient viral load on HCV transmission - univariate analysis**

<table>
<thead>
<tr>
<th></th>
<th>Cases (n =60)</th>
<th>Controls (n = 204)</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viral load</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(source)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR +</td>
<td>100.0%</td>
<td>85.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCR -</td>
<td>0.0%</td>
<td>15.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HCV viral load</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;= 4 ( \log_{10} ) cop/mL</td>
<td>8.3%</td>
<td>40.7%</td>
<td>1.0</td>
<td>0.6-55.5</td>
</tr>
<tr>
<td>4&lt; &lt;=6 ( \log_{10} ) cop/mL</td>
<td>41.7%</td>
<td>37.0%</td>
<td>5.5</td>
<td>1.1-114.1</td>
</tr>
<tr>
<td>&gt; 6 ( \log_{10} ) cop/mL</td>
<td>50.0%</td>
<td>22.2%</td>
<td>11.0</td>
<td></td>
</tr>
</tbody>
</table>

*Cases = 12, controls =27

Yazdanpanah ICAAC 2003
Higher prevalence of occult HBV in patients with HCV

- Study population:
  - 396 patients with HCV-related chronic liver disease and HBsAg-
  - 50 patients with liver disease anti-HCV-HBsAg-
- Liver biopsy and HBV DNA extraction from liver specimens

Higher prevalence of occult HBV in patients with HCV

<table>
<thead>
<tr>
<th>Patient Status</th>
<th>HBV-Positive Patients/Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HCV-positive</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-HBc-positive</td>
<td>46/100*</td>
</tr>
<tr>
<td>Anti-HBc-negative</td>
<td>20/100</td>
</tr>
<tr>
<td>Total</td>
<td>66/200†</td>
</tr>
<tr>
<td><strong>HCV-negative</strong></td>
<td></td>
</tr>
<tr>
<td>Anti-HBc-positive</td>
<td>2/7‡</td>
</tr>
<tr>
<td>Anti-HBc-negative</td>
<td>5/43</td>
</tr>
<tr>
<td>Total</td>
<td>7/50</td>
</tr>
</tbody>
</table>

HBV DNA levels in patients with occult HBV

• Quantification possible with the development of real-time highly sensitive PCR assays

• 160 anti-HBc-positive/HBsAg-negative sera collected in the diagnostic setting.
• HBV DNA detected in 12.5% of the samples.
  – 70%  < 500 geq/ml
  – 30%  500 and 63 000 geq/ml.
• Risk of detecting HBV DNA was increased by a positive HCV serostatus (OR: 5.0, 1.6–15.7)

• Risk of HBV transmission from patients (HCWs) with occult HBV?
  – reported in the past via organ and blood donations from anti-HBc-positive/HBsAg-negative donors

Matsumoto et al., Transfusion 2001
Chazouilleres et al., Lancet 1994
• Risk of HBV transmission from patients (HCWs) with occult HBV? – reported in the past via organ and blood donations from anti-HBc-positive/HBsAg-negative donors

Matsumoto et al., Transfusion 2001
Chazouilleres et al., Lancet 1994

Should HBV DNA be performed in anti-HBc-positive/HBsAg-negative HCWs infected with HCV?
HBV + HDV
Impact of HDV on HBV replication

• Cases: 65 patients with dual or triple chronic viral hepatitis
  – 25 (38%) by HBV and HCV
  – 18 (28%) by HBV and HDV
  – 22 (34%) by HBV, HCV, and HDV
• Controls: 110 patients with single virus infection:
  – 55 by HBV
  – 55 by HCV

• HBV/HDV coinfection was associated with lower HBV viremia ($2.5 \times 10^4$ copies/mL) than that found in HBV infection ($1.2 \times 10^7$ copies/mL) ($P < .05$).

Jardi et al. Hepatology 2001
Conclusion

• Scarce data on co-infection by the HBV HCV viruses in HCWs
• Co-infection by the two viruses is not uncommon.
• In general, decreased replication level of one or both viruses in cases of combined infection

“Publication bias”: decreased replication resulting in none transmission and therefore no case reports published?
Conclusion

- HBV DNA detection in HCV-infected HCW with isolated antibody to hepatitis B core should be discussed
  - High rate of positivity
  - Risk of transmission
• Anti-hepatitis B vaccination