Anti-HBc+ Liver grafts: which prophylaxis in which recipients?

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Dealing with organ shortage

✓ Despite concerted efforts to safely expand the donor organ pool, there is a widening gap between organ availability and demand.
Anti-HBc+ liver grafts represent an important resource

- One-third of the global population are or was infected with HBV\(^1,2\)
- Prevalence of anti-HBc positivity differs dramatically between regions\(^3\)

### Table 1. Published studies on the prevalence of anti-HBc positivity among liver donors in different countries.

<table>
<thead>
<tr>
<th>First author, year [Ref.]</th>
<th>Donors, (n/N) anti-HBc</th>
<th>Country</th>
<th>Positive/total</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wachs (1995) [42]</td>
<td></td>
<td>USA</td>
<td>25/1190</td>
<td>2</td>
</tr>
<tr>
<td>Dodson (1997) [29]</td>
<td></td>
<td>USA</td>
<td>70/2578</td>
<td>3</td>
</tr>
<tr>
<td>Nery (2001) [40]</td>
<td></td>
<td>USA</td>
<td>48/724</td>
<td>6</td>
</tr>
<tr>
<td>Chen (2002) [16]</td>
<td></td>
<td>Taiwan</td>
<td>24/42</td>
<td>57</td>
</tr>
</tbody>
</table>

The dilemma using anti-HBc+ liver grafts

✓ Risk of transmission
  • HBV DNA could be detected by PCR in sera or liver tissue in 5 and 50% of these donors, respectively

✓ Benefits for the recipients
  • Emergency of the liver transplantation
How to optimize the use of anti-HBc+ liver grafts?

✔ Minimizing risks

• Selection of donors
• Selection of recipients
• Suitable prophylaxis strategy

✔ Maximizing benefits
How to optimize the use of anti-HBc+ liver grafts?

- Minimizing risks
- Maximizing benefits

- **Selection of donors**
- Selection of recipients
- Suitable prophylaxis strategy
Selection of anti-HBc+ donors

✓ All donors are currently screened for HBV status
  • HBsAg
  • Anti-HBs
  • Anti-HBc

✓ HBsAg+ donors are usually not considered for LT

✓ Anti-HBc+ donors should be screened for
  • HBV DNA positivity in sera (NAT)
  • Liver fibrosis (<F2)
  • Different characteristics compared to Anti-HBc- donors? Older age?¹

✓ Anti-HBc+ liver grafts are allocated to patients who consent to receive such organs

1. Prieto M, Liver Transpl, 2001
How to optimize the use of anti-HBc+ liver grafts?

- Minimizing risks
- Maximizing benefits

- Selection of donors
- **Selection of recipients**
- Suitable prophylaxis strategy
The emergence of
- Clinical sign of hepatitis
- And/or HBsAg+
- And/or HBV DNA+
- And/or anti-HBc+

- Could reflect an occult infection but also
  - False positivity of the test
  - Transmitted antibody by the donor
  - Resolved infection
The expected spontaneous probability of *de novo* HBV infection depends on the HBV serological status of the recipient.

- **HBsAg+**: 0%
- **HBsAg-**
  - **Anti-HBc+**: 10-15%
  - **Naive**: 60-80%
The expected spontaneous probability of *de novo* HBV infection depends on the HBV serological status of the recipient.

- **Risk of *de novo* HBV infection**
  - **HBsAg+**
    - 0%
  - **HBsAg-**
    - **Anti-HBc+**
      - 10-15%
    - **Naive**
      - 60-80%

1. Skagen CL, Clinical Transpl, 2011
The expected spontaneous probability of de novo HBV infection depends on the HBV serological status of the recipient.

- **Risk of de novo HBV infection**
  - **HBsAg+**: 0%
  - **HBsAg-**
    - Anti-HBc+ **10-15%**
    - Naive **60-80%**
Anti-HBc+ recipients: the risk varies according to anti-HBs

- Heterogeneity in reporting of anti-HBs status in several studies
- Some studies suggest that the presence of anti-HBs in anti-HBc+ recipients may reduced the probability of *de novo* HBV infection but did not eliminate it\(^1\)

\(p < 0.001\) for all comparison Vs HBV naive

The expected spontaneous probability of *de novo* HBV infection depends on the HBV serological status of the recipient.

- **Risk of *de novo* HBV infection**
  - HBsAg+ 0%
  - HBsAg-
    - Anti-HBc+ 10-15%
    - Naive 60-80%
HBsAg+ recipients: HBV recurrence

- >12 studies report results on HBsAg+ patients receiving anti-HBc+ liver grafts
- Prevalence of HBV recurrence is about 11% ranged from 0 to 69%¹

Table 2. Published studies of liver transplantation using anti-HBc positive donors in HBsAg-positive recipients.

<table>
<thead>
<tr>
<th>First author, year [Ref.]</th>
<th>HBsAg positive Recipients, n</th>
<th>Anti-HBV prophylaxis</th>
<th>Follow-up (months)</th>
<th>HBV recurrence, n (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu (2001) [19]</td>
<td>6</td>
<td>HBIG</td>
<td>20</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Roque-Afonso (2002) [21]</td>
<td>4</td>
<td>HBIG</td>
<td>19</td>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>Nery (2003) [22]</td>
<td>17</td>
<td>LAM: 12, HBIG + LAM: 5</td>
<td>29</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Montalti (2004) [23]</td>
<td>26</td>
<td>HBIG ± LAM</td>
<td>NA</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Celebi-Kobak (2007) [26]</td>
<td>36</td>
<td>HBIG + LAM</td>
<td>19</td>
<td>1 (3)</td>
<td>92</td>
</tr>
</tbody>
</table>

HBsAg+ recipients: HBV recurrence

- >12 studies report results on HBsAg+ patients receiving anti-HBc+ liver grafts

- Prevalence of HBV recurrence is about 11% ranged from 0 to 69%<sup>1</sup>

- There may be an increased risk of HBV recurrence compared to anti-HBc- liver graft<sup>2</sup>

HBsAg+ recipients

✓ >12 studies report results on HBsAg+ patients receiving anti-HBc+ liver grafts

✓ Prevalence of HBV recurrence is about 11% ranged from 0 to 69%1

✓ Increased risk of HBV recurrence compared to anti-HBc- liver graft?2

✓ Anti-HBc+ grafts may have better outcomes when transplanted into HBsAg+ than HBsAg- recipients (n=219)3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD at LT</td>
<td>1.300 (per 10 units)</td>
<td>1.134 - 1.491</td>
<td>0.0002</td>
</tr>
<tr>
<td>Recipient HBsAg status (positive vs. negative)</td>
<td>0.426</td>
<td>0.304 - 0.597</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Portal vein thrombosis (yes vs. no)</td>
<td>1.988</td>
<td>1.139 - 3.496</td>
<td>0.0156</td>
</tr>
<tr>
<td>Donor HBcAb status (positive vs. negative)</td>
<td>1.555</td>
<td>1.184 - 2.042</td>
<td>0.0015</td>
</tr>
<tr>
<td>DRI</td>
<td>1.406 (per unit)</td>
<td>1.029 - 1.921</td>
<td>0.0325</td>
</tr>
</tbody>
</table>

How to optimize the use of anti-HBc+ liver grafts?

✔ Minimizing risks ✔ Maximizing benefits

- Selection of donors
- Selection of recipients
- **Suitable prophylaxis strategy**
Prophylaxis: mandatory?

✓ Prophylaxis constantly decreases the risk of *de novo* HBV infection

1. Cholongitas E, J Hepatol, 2010
Prophylaxis: mandatory?

✓ Prophylaxis constantly decreases the risk of *de novo* HBV infection

1. Chalongitas E, J Hepatol, 2010
Prophylaxis: mandatory?

✓ Prophylaxis do not show any superiority in anti-HBc+ and anti-HBs+ recipients\(^1\)

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1. Skagen CL, Clinical Transpl, 2011
Which prophylaxis?

- HBIG
- Lamivudine
  - Second generation analogues
- HBIG + antiviral
- Vaccination
  - Alone or combined
Which prophylaxis?

✓ Vaccination alone: Do not
  • One study: 100% of de novo infection\(^1\)
✓ Vaccination plus HBIG and/or antivirals: not clear if vaccination provides any advantages

1. Lee K, Transplant Proc, 2004
Which prophylaxis?

✓ Vaccination\(^1\) ?

✓ HBIG monoprophylaxis: not recommended in anti-HBs- recipients\(^2\)

Vaccination\(^1\)?

- HBIG monoprophylaxis: suboptimal strategy\(^2\)
- Antiviral agents alone or combined strategy: 32 studies (Lamivudine)

✓ Vaccination\(^1\) ?
✓ HBIG monoprophylaxis: suboptimal strategy\(^2\)
✓ Antiviral agents alone or combined strategy: 32 studies (Lamivudine)
  • According to the heterogeneity of recipients status and prophylaxis strategies, the low rate of recurrence, it is difficult to assess the superiority of a combined strategy\(^3\)

<table>
<thead>
<tr>
<th>Recipient Serology</th>
<th>LAM Alone (n)</th>
<th>Posttransplant Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>HBV Recurrence</td>
</tr>
<tr>
<td>HBsAb</td>
<td>HBcAb</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>13</td>
</tr>
<tr>
<td>+</td>
<td>−</td>
<td>25</td>
</tr>
<tr>
<td>−</td>
<td>+</td>
<td>17</td>
</tr>
<tr>
<td>−</td>
<td>−</td>
<td>18</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>73</td>
</tr>
</tbody>
</table>

Algorithm of prophylaxis strategies

- **Anti-HBc+ donors**
  - HBsAg+ recipients
    - HBIG + Antiviral
  - HBsAg- recipients
    - Naive recipients
    - Anti-HBc-Anti-HBs+
    - Anti-HBc+ Anti-HBs-
    - Anti-HBc+ Anti-HBs+
      - Antiviral*
      - Antiviral*
      - Antiviral*
      - Nothing?

*Very few data regarding other antiviral than LAM but results could probably be extrapolated
Prophylaxis could be discontinued when tapering immunosuppression but unclear

Anti-HBc+ Liver grafts: which prophylaxis in which recipients?

✓ Anti-HBc+ liver grafts represent an important resource to deal with organ shortage.
✓ The prevalence of anti-HBc positivity varies in Europe from 2 to 12%.
✓ When transplanted to a HBsAg+ recipients, the risk of recurrence exits and a combined HBIG and antiviral therapy should be done.
✓ When transplanted to HBsAg- recipients, the risk of de novo infection is different according to the serological status of the recipients (lower risk in anti-HBs+ recipients) but it is greatly diminished with prophylaxis (<5%). Antiviral therapy alone seems to be sufficient.
✓ These statements mostly coming from registry studies, retrospective studies or systematic reviews. Face to face and prospective studies are lacking and absolutely required to properly answer both questions.
Thank you!

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  B Roche
  T Antonini
  JC Duclos-Vallée
  E De Martin
  R Sobesky
  F Saliba