Hepatitis B virus and solid organ transplantation

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Conflict of interest
Outline

Hepatitis B virus

Risk of HBV infection in transplantation

Prevention of HBV infection

Management of HBV reactivation
Hepatitis B virus

- HBV is an DNA virus
- Spread through mother to child transmission, unprotected sex, blood transfusion and exposed to infected blood and body fluids
- Chronic HBV infection affects 350-400 million people worldwide
  - Causes over one million deaths per year
- Cirrhosis and hepatocellular carcinoma are frequent complications
- Common indication for liver transplantation

Jonas M. Liver Int. 2009;29 (suppl 1):133–139
Natural course of HBV infection

- **HBeAg**
- **Anti-HBe**

- **HBV DNA**
- **ALT**

- Immune tolerance phase
- Immune clearance (HBeAg-positive chronic hepatitis B)
- Inactive carrier phase
- Reactivation (HBeAg-negative chronic hepatitis)

Time (years)
## Interpretation of serologic tests for HBV

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBc IgM</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>No infection and immunity</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Natural immunity</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Vaccine immunity</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Resolving acute infection</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Resolved infection</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Chronic infection</td>
</tr>
</tbody>
</table>

Adapted from Huprikar S et al. American Journal of Transplantation 2015;15:1162-72
### Oral Anti-Viral Agents: Potency and Resistance

<table>
<thead>
<tr>
<th>Drug</th>
<th>Anti-viral potency</th>
<th>Genetic barrier</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>+++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Adefovir</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Entecavir</td>
<td>++++</td>
<td>++++</td>
<td>+++</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>++++</td>
<td>+++++</td>
<td>++</td>
</tr>
</tbody>
</table>
Risk of resistance in naïve patients
### Agents reported to cause HBV reactivation

<table>
<thead>
<tr>
<th>Class</th>
<th>Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone, methylprednisolone, prednisolone</td>
</tr>
<tr>
<td>Antitumor antibiotics</td>
<td>Actinomycin D, bleomycin, daunorubicin, doxorubicin, epirubicin, mitomycin-C</td>
</tr>
<tr>
<td>Plant alkaloids</td>
<td>Vinblastine, vincristine</td>
</tr>
<tr>
<td>Alkylating agents</td>
<td>Carboplatin, chlorambucil, cisplatin, cyclophosphamide, ifosfamide</td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Azauridine, cytarabine, fluouracil, gemcitabine, mercaptopurine, methotrexate, thioguanine</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Alemtuzumab, rituximab</td>
</tr>
<tr>
<td>Anti-TNF</td>
<td>Infliximab, etanercept, adalimumab, certolizumab, golimubab</td>
</tr>
<tr>
<td>Others</td>
<td>Colaspase, docetaxel, etoposide, fludarabine, folinic acid, interferon, procarbazine</td>
</tr>
</tbody>
</table>
Risk factors for reactivation

- Patients with cirrhosis
- HBeAg positive patients
- HBeAg negative but high HBV DNA levels (20,000 IU/mL)
- Patients with antiviral drug resistance prior to transplantation
## Impact of HBV infection on RT recipients
### Risk of mortality

<table>
<thead>
<tr>
<th>Authors</th>
<th>Adjusted RR (95% CI)</th>
<th>Country</th>
<th>Reference year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al</td>
<td>1.8 (0.9–3.4)</td>
<td>Taiwan</td>
<td>2001</td>
</tr>
<tr>
<td>Chan et al</td>
<td>9.7 (4.7–19.9)</td>
<td>Hong Kong</td>
<td>2002</td>
</tr>
<tr>
<td>Breitenfeldt et al</td>
<td>1.90 (1.8–1.9)</td>
<td>Germany</td>
<td>2002</td>
</tr>
<tr>
<td>Morales et al</td>
<td>1.57 (0.7–3.1)</td>
<td>Spain</td>
<td>2004</td>
</tr>
<tr>
<td>Ridruejo et al</td>
<td>2.50 (0.7–8.8)</td>
<td>Argentina</td>
<td>2004</td>
</tr>
<tr>
<td>Aroldi et al</td>
<td>2.36 (1.5–3.7)</td>
<td>Italy</td>
<td>2005</td>
</tr>
</tbody>
</table>

RR 2.49 (95% CI, 1.64–3.78)

## Impact of HBV infection on RT recipients

### Risk of graft loss

<table>
<thead>
<tr>
<th>Authors</th>
<th>Adjusted RR (95% CI)</th>
<th>Country</th>
<th>Reference year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsieh et al</td>
<td>0.97 (0.17–5.4)</td>
<td>Taiwan</td>
<td>2000</td>
</tr>
<tr>
<td>Lee et al</td>
<td>1.17 (0.7–3.4)</td>
<td>Taiwan</td>
<td>2001</td>
</tr>
<tr>
<td>Chan et al</td>
<td>1.0 (NA)</td>
<td>Hong Kong</td>
<td>2002</td>
</tr>
<tr>
<td>Breitenfeldt et al</td>
<td>1.66 (1.3–1.8)</td>
<td>Germany</td>
<td>2002</td>
</tr>
<tr>
<td>Morales et al</td>
<td>1.13 (0.57–2.2)</td>
<td>Spain</td>
<td>2004</td>
</tr>
<tr>
<td>Ridruejo et al</td>
<td>7.19 (2.06–25.11)</td>
<td>Argentina</td>
<td>2004</td>
</tr>
<tr>
<td>Aroldi et al</td>
<td>1.55 (1.12–2.14)</td>
<td>Italy</td>
<td>2005</td>
</tr>
</tbody>
</table>

RR 1.44 (95% CI, 1.02–2.04)
Pretransplant evaluation

- All living potential donors and recipients should be tested for HBV
- Baseline tests
  - HBsAg, Anti HBC, Anti HBs
- Further tests
  - HBeAg, Anti-HBe
  - HBV DNA
  - Liver enzymes
  - Abdominal USG
  - Assessment of liver necroinflammation and fibrosis
Vaccine schedule

- Hepatitis A
  - 2 doses given 6 months apart

- Hepatitis B
  - 3 doses given over a 6-month period
  - 0,1,6 months

- Combined Hepatitis A & B vaccine

higher dose (40 mg antigen per dose) vaccine is recommended in the pretransplant setting in hemodialysis patients and other immunocompromised hosts
Donor and recipient matching

- HBsAg (+) donor, HBsAg (±) recipient
- Anti-HBc (+) donor, HBsAg (±) recipient
- HBsAg (-) donor, HBsAg (+) recipient
Recipient of any organ from HBsAg donors

- Organs from HBsAg (+) donors may be carefully considered in all adult transplant candidates after an individualized assessment of the risk and benefits and appropriate patient consent.

- HBsAg (+) livers should only be considered when significant donor liver disease has been ruled out by histology.

- Indefinite prophylaxis with entecavir or tenofovir is recommended for all recipients.

- HBIG should be considered in all recipients when the anti-HBs titer is <100 IU/L.

- HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely.

Isolated Anti-HBc (+) and de nova HBV (DNH) in liver transplantation (LT)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Without Prophylaxis</th>
<th>With Prophylaxis (LAM and/or HBIG)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV non-immune pre-vaccinated</td>
<td>58%</td>
<td>11%</td>
</tr>
<tr>
<td>Previously vaccinated</td>
<td>18%</td>
<td>2%</td>
</tr>
<tr>
<td>Isolated anti-HBc naturally immune recipients</td>
<td>14%</td>
<td>3%</td>
</tr>
</tbody>
</table>

The reported risk of DNH in HBV naive kidney recipients ranges from 0% to 27%.

There is a low risk of transmission of HBV infection from HBsAg-negative, Anti-HBc positive donors to HBsAg negative recipients (3.2%) \( 0.011 \) (95% CI 0.0070–0.0182)

The risk is even lower if the recipient is anti-HBs positive.

HBV vaccination prior to transplant, with target anti-HBs titers \( \geq 10 \) IU/L, has been demonstrated to be protective for renal recipients of anti-HBc positive donors.

Algorithm for use of liver grafts from Anti-HBc (+) donors in recipients without chronic HBV

Donor
- Anti-HBc (+), HBsAg (-)

Recipient
- Anti-HBc (+), Anti-HBs (+)
  - Consider no prophylaxis

Recipient
- Anti-HBc (-), Anti-HBs (+)
  - Lamivudine

Recipient
- Anti-HBc (-), Anti-HBs (-)
  - HBV vaccine
  - Lamivudine

Antiviral use

- Lamivudine is recommended as the most cost effective choice for prophylaxis
- Entecavir or tenofovir may also be considered for prophylaxis due to their higher genetic barrier to resistance
- Indefinite duration of prophylaxis for non-immune recipients
- Discontinuation of prophylaxis may be considered after 1 year in recipients with confirmed persistence of immunity (anti-HBs ≥ 10 IU/mL)
- HBIG is not recommended
- HBV DNA with or without HBsAg should be monitored every 3 months for 1 year and then every 3–6 months indefinitely in all recipients regardless of current or prior prophylaxis strategy

Algorithm for use of non-liver grafts from Anti-HBc (+) donors in recipients without chronic HBV

Donor

Anti-HBc (+), HBsAg (-)

Recipient

Anti-HBc (+)
Anti-HBs (+)
No prophylaxis

Anti-HBc (-)
Anti-HBs (+)
No prophylaxis

Anti-HBc (-)
Anti-HBs (-)
HBV vaccine
May consider lamivudine for up to one year

Decompensated cirrhosis

- Risk of HBV reactivation
- LAM is not recommended
- First line agents; tenofovir, entecavir
  - Life long therapy
- With or without HBIG
- Risk of nephrotoxicity
  - Entecavir is recommended (Low risk of nephrotoxicity)
- NUCs on adjusted doses for renal function

EASL. J Hepatol 2012;57(1):167-85
CHB and renal transplantation

- All HBsAg positive case should be considered for antiviral treatment before SOT
  - Entecavir or tenofovir
- Compensated cirrhotic patients are not candidates for RT
- Cirrhotic patients with decompensated disease should be evaluated for combined liver-kidney transplantation

Ridruejo E. World J Hepatol 2015;27:189-203
Treatment algorithm for management of renal transplant candidates with CHB

HBsAg (+) & RT candidate

Pretransplant assessment

HBV DNA, HBeAg, ALT, USG, grade of liver fibrosis

Chronic hepatitis

HBV DNA undetectable
- Antiviral prophylaxis or preemptive RT

HBV DNA <2.000 IU/ml
- Antiviral prophylaxis RT

HBV DNA ≥2.000 IU/ml
- Antiviral treatment RT

Cirrhosis

Compensated
- Antiviral treatment Preclude RT

 Decompensated
- Antiviral treatment Combined transplantation

Adapted from: Tsai MC et al. World J Gastroenterol 2010;16(31):3878-87
Ridruejo E. World J Hepatol 2015;27:189-203
Treatment of HBV reactivation

- Lead to liver failure
  - The risk is higher in patients with cirrhosis
- Lead to graft lost
- Check for causes of reactivation
  - Drug noncompliance, drug resistance
- Choice of drug
  - Prior prophylactic therapy
  - Presence of drug resistance mutants
- Entecavir and/or tenofovir
Take home messages

- Reactivation of HBV may result in graft loss, liver failure and death
- Screening of recipients and donors for HBV infection prior to transplantation is recommended
  - HBsAg, Anti-HBs, Anti-HBc
- All seronegative candidates should be vaccinated against HBV
- Early implementation of antiviral prophylaxis could prevent complications
- Antiviral therapy with NUCs before transplant decreases the risk of reinfection in CHB patients
  - First line agents; entecavir and tenofovir