Management of HBV in Kidney Transplanted Patients

Dr. E. Nemati
Hepatitis B virus (HBV) infection

- Hepatitis B virus (HBV) infection confers a significantly negative impact on the clinical outcomes of kidney allograft recipients.
CHB PATIENTS BEFORE KIDNEY TRANSPLANTATION

patients, separated into three subgroups:

1. Patients with HBV-related nephropathies (membranous/membranoproliferative/IgA glomerulopathy/polyarteritis nodosa)
2. Patients receiving hemodialysis (HD)
HBV-related nephropathie

- Patients with HBV-related nephropathies, in which kidney disease is induced via the immune-complex, may respond highly to antiviral therapy, while those who need immunosuppressive therapy ideally should start antiviral treatment one month before treatment, continued for at least 12 mo after last dose of immunosuppressive drug.
HBV carrier rate

- HBV carrier rate in the general population can exceed 10%.

- The reported prevalence of HBV infection among dialysis patients in the United States is often below 1.0%,

- Prevalence rate is between 7.0% and 15% in the Asian-Pacific region.

- Prevalence of Chronic HBV Infection in general Population is 1.7% to 8.9% in Iran in 2005.
Frequency of hepatitis B surface antigen-positivity in renal transplant recipients

<table>
<thead>
<tr>
<th>Authors</th>
<th>HBsAg rate, % (n)</th>
<th>Reference year</th>
<th>Country of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu et al[10]</td>
<td>20.9 (14/67)</td>
<td>1994</td>
<td>Taiwan (China)</td>
</tr>
<tr>
<td>Mathurin et al[3]</td>
<td>15.3 (128/834)</td>
<td>1999</td>
<td>France</td>
</tr>
<tr>
<td>Lee et al[4]</td>
<td>12.9 (62/477)</td>
<td>2001</td>
<td>Taiwan (China)</td>
</tr>
<tr>
<td>Chan et al[30]</td>
<td>13.2 (67/509)</td>
<td>2002</td>
<td>Hong Kong (China)</td>
</tr>
<tr>
<td>Morales et al[8]</td>
<td>2.2 (76/3365)</td>
<td>2004</td>
<td>Spain</td>
</tr>
<tr>
<td>Aroldi et al[20]</td>
<td>14.2 (77/541)</td>
<td>2005</td>
<td>Italy</td>
</tr>
<tr>
<td>Santos et al[7]</td>
<td>3 (37/1224)</td>
<td>2009</td>
<td>Portugal</td>
</tr>
<tr>
<td>Tsai et al[9]</td>
<td>9.2 (51/554)</td>
<td>2009</td>
<td>Taiwan (China)</td>
</tr>
</tbody>
</table>
Vaccination

- An effective immunization program in dialysis and CKD patients is the cornerstone to prevent de novo HBV infection in renal transplant recipients.

- HBV vaccination should be given early in the course of chronic kidney disease.
## Doses and Schedules: Hepatitis B Vaccines for Hemodialysis Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>Recombivax HB</th>
<th>Engerix B</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Dose</td>
<td>Volume</td>
<td>Schedule</td>
<td>Dose</td>
</tr>
<tr>
<td>≥20 years of age: Predialysis*</td>
<td>10 µg</td>
<td>1.0 mL</td>
<td>3 doses at 0, 1, &amp; 6 months</td>
<td>20 µg</td>
</tr>
<tr>
<td>≥20 years of age: Dialysis-dependent</td>
<td>40 µg</td>
<td>1.0 mL</td>
<td>3 doses at 0, 1, &amp; 6 months</td>
<td>40 µg</td>
</tr>
<tr>
<td>&lt;20 years of age*</td>
<td>5 µg</td>
<td>0.5 mL</td>
<td>3 doses at 0, 1, &amp; 6 months</td>
<td>10 µg</td>
</tr>
</tbody>
</table>
Course of chronic HBV infection

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

**Stages**:
- Immune tolerant
- Immune clearance HBeAg-positive chronic hepatitis
- Inactive carrier state
- Reactivation HBeAg-negative chronic hepatitis

**Markers**:
- HBeAg
- Anti-HBe
HBV transmission

- The possibility of HBV transmission by organ transplantation can be predicted from the serological status of both donor and recipient.

- It is generally accepted that transplanting an HBsAg-positive allograft into an HBsAg-negative recipient carries a significant risk of de novo infection.
There are two principal approaches to prevent HBV reactivation after renal transplantation: prophylactic preemptive strategies.
Time of presentation of common viral illnesses post-transplant.

<table>
<thead>
<tr>
<th>Time Frame</th>
<th>Illnesses</th>
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<tbody>
<tr>
<td>First Month</td>
<td></td>
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<tr>
<td>Months 1-3</td>
<td></td>
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<tr>
<td>Months 3-6</td>
<td></td>
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<tr>
<td>Months 6-12</td>
<td></td>
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<tr>
<td>Beyond 1 year</td>
<td></td>
</tr>
<tr>
<td>Cytomegalovirus</td>
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</table>

**Herpes Simplex Virus**

- Varicella Zoster Virus
- Epstein Barr Virus/PTLD

**HHV-6/HHV-7**

- HHV-8

**BK/ JC Virus**

- Hepatitis B/Hepatitis C (acquisition of new infection)

**Hepatitis B/C (reactivation)**

- Adenovirus/RSV/Parainfluenza/HMPV/Influenza/Coronavirus/Enterovirus

**WNV (acquisition from transplant)**

- WNV (acquired after transplant)

**Abbreviations:** PTLD = Post Transplant Lymphoproliferative Disorder, HHV = Human Herpes Virus, RSV = Respiratory Syncitial Virus, HMPV = Human Metapneumovirus, WNV = West Nile Virus

**Key:**

- ***** = onset of Cytomegalovirus disease in absence of prophylaxis**
- **### = onset of Cytomegalovirus disease in setting of extended prophylaxis**
- **----- = less commonly, Varicella Zoster infection can present beyond 6 months**
- **+++ = less commonly, BK virus infection can present in months 1**

Blair C. Weikert, and Emily A. Blumberg CJASN 2008;3:S76-S86
Different Causes and Forms of HBV Reactivation

- Spontaneous
- Progressive Immunodeficiency (HIV Infection)
- Sudden Withdrawal of Antiviral Therapy
- Cancer Chemotherapy
- Immunosuppression for Autoimmune or Allergic Conditions
- Solid Organ Transplantation (Kidney, Heart, Lung)
- Liver Transplantation (Reactivation in Graft)
- Bone Marrow Transplantation
The clinical course of patient 12.

Contribute to the progression of liver disease

In chronic HBV patients,

1. Viral factors (viral load, genotype and genomic mutations)
2. Host factors (age, sex, and immune status)
3. Other factors (alcohol consumption, cigarette smoking, exposure to aflatoxin, and other viral superinfections)
HBsAg + RT candidate

Pretransplant assessment including HBV DNA, HBeAg status, grading of liver fibrosis (liver biopsy or non-invasive)

- HBV DNA undetectable
  - Prophylactic therapy
- HBV DNA < 2000 IU/mL
  - Preemptive therapy
- HBV DNA > 2000 IU/mL
  - Treatment

Decompensated liver disease

Assess for combined LRT
All RRT patients

Check HBsAg, Anti-HBc and Anti-HBs
If HBsAg-ve and anti-HBs-ve: HBV vaccination

HBsAg+ donor → HBsAg- recipient

Only when recipient is anti-HBs+ve
Pre-operative HBIG
Anti-viral Rx to donor and recipient if donor HBV DNA+ or HBeAg+
Repeat HBV serology after transplantation
HBsAg-positive donors in HBsAb-positive recipients

400 U HBIG weekly for 3 mo and lamivudine 100 mg daily for 6 mo for recipients with HBV DNA-positive grafts), there was no significant difference in liver injury and patient survival. HBV viral status should be monitored.
Interferon (IFN) use has been limited to young patients with HBV-related glomerulopathy without cirrhosis, psychosis or autoimmune disease.

IFN has been poorly tolerated by patients with CKD, has shown relatively low efficacy and has set RT recipients under the risk of acute rejection, and thus, it is contraindicated.
Nucleoside analogues

- With the advent of oral nucleoside/tide analogues which suppress HBV replication effectively.
- The current options of nucleoside/tide analogues include:
  - lamivudine, entecavir, telbivudine, adefovir
tenofovir
## Approved Oral Antiviral Agents for HBV

<table>
<thead>
<tr>
<th></th>
<th>Lamivudine</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric approval</strong></td>
<td>2001</td>
<td>2008</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>Age 2-17</td>
<td>Age 12-17</td>
<td>Age &gt; 16</td>
<td>Age ≥ 16</td>
<td>Age ≥ 18</td>
</tr>
<tr>
<td><strong>Dose (mg/day)</strong></td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
<td>Renal</td>
</tr>
<tr>
<td><strong>GFR &gt; 50 mL/min</strong></td>
<td>100 mg/day†</td>
<td>10 mg/day</td>
<td>0.5 mg/day†</td>
<td>600 mg/day</td>
<td>300 mg/day</td>
</tr>
<tr>
<td><strong>30-49 mL/min</strong></td>
<td>50 mg/day</td>
<td>10 mg/day</td>
<td>0.25 mg/day or 0.50/m/every 2nd day</td>
<td>600 mg/every 2nd day</td>
<td>q 48 hours</td>
</tr>
<tr>
<td><strong>10-29 mL/min</strong></td>
<td>15-25 mg/day</td>
<td>10 mg/every 2nd day</td>
<td>0.15 mg/day or 0.50/m/every 3rd day</td>
<td>600 mg/every 3rd day</td>
<td>q 72-96 hrs</td>
</tr>
<tr>
<td><strong>Dialysis</strong></td>
<td>10 mg/day</td>
<td>10 mg/—week</td>
<td>0.05 mg/day or 0.50/m/week</td>
<td>600 mg/week</td>
<td>weekly</td>
</tr>
<tr>
<td><strong>Potential side effects</strong></td>
<td>Nephrotoxicity at high doses</td>
<td>? Solid tumors in animal models</td>
<td>Nephrotoxicity</td>
<td>Nephrotoxicity in animal models</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects in licensing trials at 1 year</strong></td>
<td>Similar to placebo</td>
<td>Similar to placebo</td>
<td>Similar to lamivudine</td>
<td>Grade 3/4 CPK 7% 1 year 12% 2 years</td>
<td>Similar to adefovir</td>
</tr>
<tr>
<td><strong>Post-marketing Adverse events</strong></td>
<td>Rare myopathy, neuropathy, pancreatitis</td>
<td>Nephrotoxicity in 3%-8% at 5 years</td>
<td>Negligible</td>
<td>Myopathy</td>
<td>Nephrotoxicity</td>
</tr>
<tr>
<td><strong>Pregnancy category</strong></td>
<td>C</td>
<td>C</td>
<td>C</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td><strong>Detection in human breast milk</strong></td>
<td>Yes</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Yes (in rats)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*1.0 mg tablets of entecavir are approved for patients with lamivudine-resistant HBV.

†Oral elixir available. For lamivudine, use 15 mg/day if GFR is 5-14 mL/minute and 25 mg/day if GFR is 15-29 mL/minute.
Lamivudine

- Lamivudine is the first amongst of drugs available for clinical use, it has the majority of data on the management of HBsAg-positive renal transplant recipients.

- Effective in suppressing HBV DNA and improving liver transaminase levels.
Lamivudine

- Prolonged treatment with lamivudine is associated with progressive increase in drug resistance and the cumulative probability of developing lamivudine resistance was approximately 60% after 69 mo.

- The emergence of lamivudine resistance can be associated with liver dysfunction,
Adefovir as a Novel Drug for the Treatment of Chronic Hepatitis B in Patients with End-Stage Renal Disease and Kidney Recipients

Seyed Mohammadehdi Hosseini Moghaddam*, Elham Iran Pour

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Adefovir


- Adefovir is a nucleotide analog of adenosine monophosphate (dAMP).
- It is a selective reverse transcriptase inhibitor of HBV-DNA replication.
- Adefovir dipivoxil (ADV) is an oral prodrug of adefovir which is used against HBV and some other viruses.
Adefovir

Adefovir has similar activity against both wild-type and lamivudine-resistant HBV.

- It is excreted in the urine through Glomerular filtration and tubular secretion unchanged. This drug is nephrotoxic.
Liver complications such as hepatic failure, liver dysfunction and an increase in aminotransaminases were reported.

Lactic acidosis and severe hepatomegaly with steatosis obesity Hepatitis exacerbation, hepatic function should be monitored.
Evidence of nephrotoxicity was observed in 30%-50% of renal allograft recipients despite dosage adjustment, and could necessitate treatment discontinuation.

Hypophosphatemia compensated with oral phosphate supplements.

Using adefovir in patients with creatinine clearances above 40 mL/min appeared safe.
ADEFOVIR & COMPLICATIONS

- Dermatologic complications like itching and rash.
- Gastrointestinal complications including abdominal pain, diarrhea, flatulence, indigestion, nausea, vomiting and dyspepsia.
- Neurologic complications like asthenia and headache have been reported.
- Respiratory complications including cough, pharyngitis, sinusitis and fever were observed.
### Entecavir and Telbivudine

- **Entecavir is effective in the treatment or lamivudine-resistant patients.**
- **ETV is considered the first choice, in patients with CKD**
- **Telbivudine is the best option when patients present low creatinine clearance and low viremia levels.**
Entecavir (ETV) Conclusion

- ETV is effective in treating chronic hepatitis B in RTRs.
- ETV is safe with regards to renal graft function, lactic acidosis, myopathy and virological resistance.
Tenofovir

- Tenofovir high efficacy in the treatment or lamivudine-resistant HBV infection.
- TDF use, few cases of osteomalacia and Fanconi syndrome have been documented.
Comparison of Adefovir and Tenofovir in the Treatment of Lamivudine-Resistant Hepatitis B Virus Infection

Florian van Bömmel,1 Thomas Wünsche,2 Stefan Mauss,3 Petra Reinke,4 Alexandra Bergk,1 Dirk Schürmann,2 Bertram Wiedenmann,1 and Thomas Berg1
Review article: nucleos(t)ide analogues in patients with chronic hepatitis B virus infection and chronic kidney disease

Alimentary Pharmacology & Therapeutics
Volume 39, Issue 1, pages 35-46, 29 OCT 2013 DOI: 10.1111/apt.12538
Duration of treatment

- With baseline HBV DNA < 2000 IU/mL, antiviral therapy should be continued for 6 mo after completion of immunosuppressive therapy.

- In patients with baseline HBV DNA ≥2000 IU/mL level, treatment should be continued until the endpoints are reached.
Duration of treatment

- Withdrawal of NAs is associated with a high risk of relapse, replication of the wild strain, and liver failure, all of which suggest prolonged therapy is necessary.

- During therapy with antivirals, measure HBV DNA and ALT levels every 3 months to monitor efficacy and to detect drug resistance.
Definition of response to nucleos(t)ide analogue antiviral therapy of chronic hepatitis B

<table>
<thead>
<tr>
<th>Category of response</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biochemical (BR)</td>
<td>Decrease in serum ALT to within the normal range.</td>
</tr>
<tr>
<td>Virologic (VR)</td>
<td>Decrease in serum HBV DNA to undetectable levels by PCR assays, and loss of HBeAg in patients who were initially HBeAg positive.</td>
</tr>
<tr>
<td><strong>Primary non-response</strong></td>
<td>Decrease in serum HBV DNA by 2 log10 IU/mL after at least 24 wk of therapy.</td>
</tr>
<tr>
<td>Virologic relapse</td>
<td>Increase in serum HBV DNA of 1 log10 IU/mL after discontinuation of treatment in at least two determinations more than 4 wk apart.</td>
</tr>
<tr>
<td>Histologic (HR)</td>
<td>Decrease in histology activity index by at least 2 points and no worsening of fibrosis score compared to pre-treatment liver biopsy.</td>
</tr>
<tr>
<td>Complete (CR)</td>
<td>Fulfill criteria of biochemical and virological response and loss of HBsAg.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time of assessment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>On-therapy</td>
<td>During therapy.</td>
</tr>
<tr>
<td>Maintained</td>
<td>Persist throughout the course of treatment.</td>
</tr>
<tr>
<td>End-of-treatment</td>
<td>At the end of a defined course of therapy.</td>
</tr>
<tr>
<td>Off-therapy</td>
<td>After discontinuation of therapy.</td>
</tr>
<tr>
<td>Sustained (SR-6)</td>
<td>6 mo after discontinuation of therapy.</td>
</tr>
<tr>
<td>Sustained (SR-12)</td>
<td>12 mo after discontinuation of therapy.</td>
</tr>
</tbody>
</table>
Hepatic complications

Attributed to increased hepatic complications such as:

- Chronic hepatitis
- Cirrhosis
- Fibrosing cholestatic hepatitis
- Hepatocellular carcinoma.
Survival after renal transplantation

- In a meta-analysis of six observational studies, HBsAg positivity was associated with a 2.49-fold risk of death after renal transplantation.


- Liver-related complications were significantly increased in subjects with detectable serum HBV DNA or were HBeAg-positive.
The Impact of Hepatitis B Infection on Outcome of Kidney Transplantation: A Long-Term Study

B. Einollahi,1* S. M. Alavian,2 M. Lessan-Pezeshki,3 N. Simforoosh,4 M. H. Nourbala,1 Z. Rostami,1 V. Pourfarziani,1 E. Nemati,1 M. Sharafi,1 M. Nafar,4 F. Pour-Reza Gholi,4 A. Firoozan4

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4Renal Transplantation Center, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran
<table>
<thead>
<tr>
<th>Graft Survival</th>
<th>Only HBsAg⁺</th>
<th>HBsAg⁺ and HCV Ab⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>One year (%)</td>
<td>91</td>
<td>70</td>
</tr>
<tr>
<td>Five years (%)</td>
<td>77</td>
<td>56</td>
</tr>
<tr>
<td>Ten years (%)</td>
<td>62</td>
<td>28</td>
</tr>
<tr>
<td>We suggest that any currently available induction and maintenance immunosuppressive medication can be used in HBV-infected KTRs.</td>
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<tr>
<td>---</td>
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<tr>
<td>We suggest that interferon treatment should generally be avoided in HBV-infected KTRs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>We suggest that all HBsAg-positive KTRs receive prophylaxis with tenofovir, entecavir, or lamivudine.</td>
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</tbody>
</table>
THANK YOU