Hepatitis B Reactivation and Hemodialysis-Related Transmission

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Hepatitis B Virus (HBV)

- **Acute HBV**
  - 2,890 reported cases in U.S. (2011)
  - 74 reported cases in NC (2013)
  - Many asymptomatic or never reported
  - Incidence highest among adults, especially males 25–44 years

- **Chronic HBV**
  - ~800,000–1.4 million people in U.S.
  - ~25,000-43,000 people in NC

http://www.cdc.gov/hepatitis/HBV/HBVfaq.htm
Acute HBV: Surveillance Case Definition

- **Clinical:** Acute illness with discrete onset of sign or symptom* consistent with acute viral hepatitis, and either
  - Jaundice, or
  - ALT >100 IU/L

- **Laboratory:**
  - Hepatitis B surface antigen (HBsAg) positive, and
  - Immunoglobulin M (IgM) antibody to hepatitis B core antigen (IgM anti-HBc) positive (if done)

*A documented negative HBsAg result within 6 months prior to a positive test for HBsAg, hepatitis B “e” antigen (HBeAg), or HBV DNA does not require acute clinical presentation to meet surveillance case definition

http://wwwn.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=711&DatePub=1/1/2012%2012:00:00%20AM
Chronic HBV: Surveillance Case Definition

- **Clinical:** No symptoms required

- **Laboratory:**
  - IgM anti-HBc negative AND a positive result on one of the following tests:
    - HBsAg, or
    - Hepatitis B e antigen (HBeAg), or
    - Nucleic acid test for HBV DNA
  - OR
  - HBsAg positive or nucleic acid test for HBV DNA positive or HBeAg positive 2 times at least 6 months apart

http://wwwn.cdc.gov/NNDSS/script/casedef.aspx?CondYrID=715&DatePub=1/1/2012%2012:00:00%20AM
Healthcare-Associated Transmission of Viral Hepatitis

- **Common exposures**
  - Unsafe injection practices
    - Syringe reuse
    - Misuse of single-dose/single-use vials
    - Failure to use aseptic technique
  - Unsafety diabetes care
  - Other lapses in infection control

- **35 healthcare-associated hepatitis outbreaks reported to CDC (2008–2012)**
  - 33 (94%) in non-hospital settings
    - Assisted living and skilled nursing facilities
    - Dental clinic
    - Outpatient clinics
    - Hemodialysis (HD) facilities
Routes of Viral Hepatitis Transmission in Healthcare Settings

- Patient to patient
- Healthcare worker to patient
- Patient to healthcare worker
Viral Hepatitis in HD Setting

- Repeated opportunities for transmission
- Can be transmitted despite no visible blood
- Hepatitis B and C viruses survive on surfaces
  - HD chairs
  - HD machines
HBV in HD Setting

- Present in high titers in blood
- Environmental contamination
- HBV-infected patients dialyze in isolation
  - Separate room, machine, equipment, and supplies
  - Designated staff

![Image of safety guidelines poster]
Transmission of HBV in HD Setting

- Failure to isolate infected patients
- Sharing staff, equipment, and supplies
- Failure to vaccinate susceptible patients
## Reported HBV Transmission Events in HD Setting, United States

<table>
<thead>
<tr>
<th>Location</th>
<th>Time period</th>
<th>Likely mode(s) of transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nebraska</td>
<td>March–June 1994</td>
<td>• Shared staff</td>
</tr>
<tr>
<td>Texas</td>
<td>April–May 1994</td>
<td>• Inadequate hand washing and glove changing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Adjacent clean and contaminated supply areas</td>
</tr>
<tr>
<td>California (1)</td>
<td>April–June 1994</td>
<td>• Multidose vials</td>
</tr>
<tr>
<td>California (2)</td>
<td>June–August 1994</td>
<td>• Undetermined</td>
</tr>
<tr>
<td>California (3)</td>
<td>June–August 1994</td>
<td>• Shared staff, equipment, and supplies</td>
</tr>
<tr>
<td>Pennsylvania</td>
<td>December 1995–May 1996</td>
<td>• Shared supplies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Multidose vials</td>
</tr>
</tbody>
</table>

CDC. Outbreaks of hepatitis B virus infection among hemodialysis patients—California, Nebraska, and Texas, 1994. MMWR 1996;45,14.
Guidelines for HBV Testing in HD Setting

- **On admission:**
  - HBsAg
  - Anti-HBc
  - Anti-HBs

- **HBV-susceptible (including nonresponders):**
  - HBsAg – Monthly

- **Anti-HBs positive (>10 mIU/mL) and anti-HBc negative:**
  - Anti-HBs – Annually

- **Anti-HBs positive and anti-HBc positive:**
  - No additional HBV testing
# HBV Vaccine Schedule for HD Patients

## TABLE 3. Doses and schedules of licensed hepatitis B vaccines for hemodialysis patients and staff members

<table>
<thead>
<tr>
<th>Group</th>
<th><strong>Recombivax HB™</strong></th>
<th></th>
<th></th>
<th><strong>Engerix-B®†</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Dose</strong></td>
<td><strong>Volume</strong></td>
<td><strong>Schedule</strong></td>
<td><strong>Dose</strong></td>
<td><strong>Volume</strong></td>
<td><strong>Schedule</strong></td>
</tr>
<tr>
<td>Patients aged ≥20 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predialysis§</td>
<td>10 µg</td>
<td>1.0 mL</td>
<td>0, 1, and 6 months</td>
<td>20 µg</td>
<td>1.0 mL</td>
<td>0, 1, and 6 months</td>
</tr>
<tr>
<td>Dialysis-dependent</td>
<td>40 µg</td>
<td>1.0 mL‡</td>
<td>0, 1, and 6 months</td>
<td>40 µg</td>
<td>2–1.0 mL doses at one site</td>
<td>0, 1, 2, and 6 months</td>
</tr>
<tr>
<td>Patients aged &lt;20 years**</td>
<td>5 µg</td>
<td>0.5 mL</td>
<td>0, 1, and 6 months</td>
<td>10 µg</td>
<td>0.5 mL</td>
<td>0, 1, and 6 months</td>
</tr>
<tr>
<td>Staff members aged ≥20 years</td>
<td>10 µg</td>
<td>1.0 mL</td>
<td>0, 1, and 6 months</td>
<td>20 µg</td>
<td>1.0 mL</td>
<td>0, 1, and 6 months</td>
</tr>
</tbody>
</table>

† SmithKline Beecham Biologicals, Philadelphia, Pennsylvania.
§ Immunogenicity might depend on degree of renal insufficiency.
¶ Special formulation.
** Doses for all persons aged <20 years approved by the U.S. Food and Drug Administration; for hemodialysis patients, higher doses might be more immunogenic.

**Note:** All doses should be administered in the deltoid by the intramuscular route.

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CDC. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR 2001;50:RR-5.
Nonresponders to HBV Vaccination

- Anti-HBs (≤10 mIU/mL)
- After 2 courses, additional doses not likely to induce antibody response

CDC. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR 2001;50:RR-5.
Maintaining Protective Levels of anti-HBs

- Booster doses when anti-HBs levels <10 mIU/mL
- No documented HBV infections among vaccinated HD patients with protective anti-HBs levels
- Outbreaks among unvaccinated and under-vaccinated HD patients can occur

CDC. Recommendations for preventing transmission of infections among chronic hemodialysis patients. MMWR 2001;50:RR-5.
HBV Reactivation

- HBV persists in hepatocytes, even in patients with resolved infection
- Moderate immunosuppression may lead to renewed HBV replication in persons with inactive chronic infection
- Severe immunosuppression may lead to reactivation of HBV replication in persons with resolved infection
- HBV reactivation and subsequent transmission in U.S. HD setting not previously described
Immunosuppression and HBV Testing

- 2008 CDC guidelines recommend HBV testing in immunosuppressed patients
  - Transplant patients
  - Patients receiving immunosuppressive therapy
  - HIV-positive patients
Public Health Notification

- March 27, 2013
- Guilford County Health Department notified via electronic laboratory report of new HBV infection
  - HD patient with no other identified risk factors
- Epidemiologic investigation began...
Objectives

- Establish source of HBV infection
- Identify other exposed patients
- Prevent additional infections
Methods

- Reviewed medical and laboratory records
- Interviewed index patient (Patient 1)
- Observed infection control practices at HD facility
- Performed HBV molecular testing
- Requested additional laboratory testing of some patients
Patient 1

- 81 year-old woman
- Risk factors for acute HBV infection:

<table>
<thead>
<tr>
<th>Present</th>
<th>Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis</td>
<td>Injection drug use</td>
</tr>
<tr>
<td></td>
<td>Tattoo or piercing</td>
</tr>
<tr>
<td></td>
<td>Contact with HBV-infected</td>
</tr>
<tr>
<td></td>
<td>Communal living</td>
</tr>
</tbody>
</table>

- Non-responder to HBV vaccination
- Anti-HBc negative
- HBsAg negative
Patient 2

- 46 year-old man
- Diagnosed with acute HBV in 1989
  - Serologic evidence of resolution and immunity
- Diagnosed with HIV in 1997
  - Antiretroviral therapy (ART) since 1999
**Timelines of HBV serology results**

### Patient 1

- **Anti-HBc-** (May 2012)
- **HBsAg-** (March 2013)
- **HBsAg+**
- **Anti-HBc+**
- **Anti-HBs+/−**
- **HepBe Ag+**
- **high HepB VL** (May 2013)
- **HD in isolation**

- **Began HD** (2011)

### Patient 2

- **HBsAg-**
- **Anti-HBc+**
- **Anti-HBs+** (2002—2011)
- **Anti-HBs-/+** (May 2012—Mar 2013)
- **HBsAg+/−** (Feb 22, 2013)
- **HBsAg+/- Anti-HBc+ Anti-HBs+/− HepBe Ag+ high HepB VL** (May 2013)
- **HD in isolation**

- **Began HD** (2011)
- **Renal transplant; Immunosuppression; Change in ART** (Nov 2011)
- **Transplant failure, Return to HD** (May 2012)
- **HBV vaccine** (Feb 2013)

- **HD in isolation**

*Anti-retroviral therapy*
Case Finding

- HBV serology identified no new infections among other patients during the risk period, May 2012-May 2013
- Only Patients 1 and 2
Infection Control Observations

- HD stations not thoroughly disinfected
- Materials carried from HD station to station
- Medication preparation cart close to HD stations
**Timelines of HBV serology results**

**Patient 1**
- Anti-HBc- (May 2012)
- HBsAg- (March 2013)
- Began HD (2011)
- HBsAg+ (Apr 2013)

**Patient 2**
- HBsAg-, Anti-HBc+, Anti-HBs+ (2002—2011)
- Anti-HBs-/+ (May 2012—Mar 2013)
- HBsAg+ (Apr 2013)
- HBsAg+/- Anti-HBc+ Anti-HBs+/- HepBe Ag+ high HepB VL (May 2013)
- HD in isolation

- Renal transplant; Immunosuppression; Change in ART* (Nov 2011)
- Transplant failure, Return to HD (May 2012)
- HBV vaccine (Feb 2013)
- HD in isolation

*Anti-retroviral therapy
Molecular testing of HBV from Patients 1 and 2

- July 2013
- Viral loads >110,000,000 IU/ml
- Whole genome sequences indicated 99.9% genetic homology
Limitations

- Observations at site visit might not fully reflect practices
- Not able to precisely determine HBV transmission time interval
Timelines of HBV serology results

**Patient 1**
- **HBsAg-** (May 2012)
- **Anti-HBc-** (May 2012)
- **Began HD** (2011)
- **HBsAg+** (March 2013)
- **HD in isolation**

**Patient 2**
- **HBsAg-**
  - **Anti-HBc+**
  - **Anti-HBs+** (2002—2011)
- **Anti-HBc-** (May 2012)
- **Anti-HBs-/+** (May 2012—Mar 2013)
- **HBsAg+/-** (Feb 22, 2013)
  - **HBsAg+** (Apr 2013)
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  - **HD in isolation**
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Timelines of HBV serology results

**Patient 1**
- HBsAg- Anti-HBc- (May 2012)
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- Began HD (2011)
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**Patient 2**
- HBsAg- Anti-HBc+ Anti-HBs+ (2002—2011)
- Anti-HBs-/+ (May 2012—Mar 2013)
- HBsAg+/-(Feb 22, 2013)
- HBsAg+/- Anti-HBc+ Anti-HBs+/- HepBe Ag+ high HepB VL (May 2013)
- HBsAg+ Anti-HBc+ (June 2013)
- Renal transplant; Immunosuppression; Change in ART* (Nov 2011)
- Transplant failure, Return to HD (May 2012)
- HBV vaccine (Feb 2013)
- HD in isolation

*Anti-retroviral therapy
Conclusions

- HBV transmission occurred after reactivated infection
- 1st reported HD-related HBV transmission in U.S. since 1996
- Only reported HD-related transmission due to HBV reactivation
Discussion

- Challenges in identification and isolation of HD patients with reactivated HBV infection
- Consideration of frequent monitoring for HBV reactivation if severe immunosuppression occurs