Transfusion-Transmitted Viral Infections

E.L. Murphy

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Prepared as part of an education project of the Global Health Education Consortium and collaborating partners
Learning objectives

1. Understand the epidemiology and clinical aspects of transfusion-transmitted viral infections (TTVI).
2. Understand how proper selection and exclusion of prospective blood donors is important.
3. Understand the advantages and limitations of blood testing strategies in maintaining blood safety.
4. Understand why the avoidance of unnecessary transfusions is important.
Hepatitis A virus (HAV)

- Predominantly spread via fecal-oral route; outbreaks often related to food handling.
- Clinical disease usually mild and self-limited, but may rarely cause severe hepatitis and death.
- Only rare cases of transfusion-transmitted infection have been reported.
- Prospective donors with a history of adult hepatitis or jaundice are excluded; no specific blood testing for HAV.
Hepatitis B virus (HBV)

Epidemiology

- Highly prevalent in Africa and Asia
- Prevalence of antibody rises with age
- Transmission by mother-to-child, sexual and blood-borne routes (injection drug use, unsterile injections, tattoos, etc.)
- HBV vaccine given to newborns can interrupt endemic cycle of transmission
Hepatitis B virus (HBV): Acute infection

In acute (self-limited) HBV infection, hepatitis B surface antigen (HBsAg) develops early in acute hepatitis and wanes by 3-4 months. Hepatitis B core antibody (anti-HBc) develops next; first IgM then IgG. Hepatitis B surface antibody (anti-HBs) develops after the disappearance of HBsAg in patients who do not become chronic carriers, and indicates recovery and persistent immunity.
In chronic HBV infection, HBsAg remains elevated and anti-HBs does not develop. The presence of HBsAg for longer than 6 months generally indicates chronic infection or HBV carrier state; the patient’s blood and body fluids are infectious.
How to interpret HBV tests

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
<th>IgM anti-HBc</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td></td>
<td>Susceptible</td>
</tr>
<tr>
<td>Neg</td>
<td>Pos</td>
<td>Pos</td>
<td></td>
<td>Immune post natural infection</td>
</tr>
<tr>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td></td>
<td>Immune post vaccination</td>
</tr>
<tr>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Pos</td>
<td>Acute infection</td>
</tr>
<tr>
<td>Pos</td>
<td>Pos</td>
<td>Neg</td>
<td>Neg</td>
<td>Chronic infection</td>
</tr>
<tr>
<td>Neg</td>
<td>Pos</td>
<td>Neg</td>
<td></td>
<td>Various (see notes)</td>
</tr>
</tbody>
</table>

Possible interpretations for solitary anti-HBc seropositivity (NEG HBsAg and anti-HBs) include:
1. recovering from acute HBV infection (anti-HBs has not yet developed)
2. distant immunity (very low levels of anti-HBs)
3. susceptible to HBV (false positive anti-HBC test)
4. low-level chronic infection (undetectable HBsAg but HBV DNA present)
Hepatitis B virus (HBV)

Acute Infection

• Incubation period 8 to 12 weeks
• Often asymptomatic; jaundice in 30 percent; fulminant hepatitis and death in <= 1 percent; supportive care but no specific treatment.
• Resolution and viral clearance indicated by conversion from surface antigen (HBsAg) to antibody (anti-HBs) reactivity.
• Chronic infection (+ HBsAg) in many infant infections but <= 5 percent of adult infections
Hepatitis B virus (HBV)

Chronic HBV infection:

- Linked to:
  - Cirrhosis
  - Hepatocellular carcinoma
- Treatment:
  - Interferon alpha-2b X 4-6 months
  - Lamivudine X 12 months
Hepatitis B virus (HBV)  
Blood Safety

Donor Exclusion:

- History of injection drug use, or sex with an IDU
- History of hepatitis or jaundice

Donor testing:

- HBsAg (all settings)
- Anti-HB core (in some countries with low prevalence)
- HBV nucleic acid testing (NAT) (see next slide)
Hepatitis B virus (HBV) Nucleic Acid Testing (NAT)

- Detects HBV DNA in chronic carriers
- Potentially more sensitive than HBsAg
- Useful in high prevalence HBV areas where anti-HBc testing is not feasible
- However HBV DNA infectious at very low levels.....

THEREFORE
- "Minipool" testing of 16 or 24 NOT defensible
- Individual donation testing laborious and expensive
Hepatitis B virus (HBV) Vaccine

- Recombinant HBV antigen vaccine is safe and effective
- Three injections at 0, 1 and 6 months
- Produces lasting anti-HBs antibody and immunity in most recipients
- Indications:
  - in developed countries, exposure to sexual or parenteral risks, health care workers
  - in HBV endemic countries, vaccination of all infants at birth
Hepatitis C Virus (HCV) Epidemiology

- Uniform worldwide prevalence of 1-2 percent; hotspots in Egypt, Japan, some African countries
- In USA and Europe, highest prevalence in age 30-50 males; probably from IDU epidemic in 1960-70’s.
- In Japan, older age cohort indicative of epidemic beginning in 1930’s (parenteral, transfusion ?)
- Parenteral transmission is by far most common (IDU, unsterile injections)
- Sexual transmission rare (e.g. sex partner of IDU)
Natural history of HCV infection. HCV RNA is detectable by sensitive assays within 10 to 11 days after infection, earlier by individual (ID) than by mini-pool (MP) testing. Clinical disease and ALT elevation occur about 2 months after infection, followed thereafter by the development of HCV antibody at 70 days with the current (3rd generation) enzyme immunoassay tests. Note the long “window period” between RNA and antibody detection, accounting for the major reduction in HCV transmission (more than for HBV or HIV) attributable to RNA testing by blood banks of potentially acute HCV infections. Over the years following acute infection, HCV RNA is thought to disappear in about 20% of patients, followed thereafter by resolution of anti-HCV.
HCV: Clinical Aspects

• Chronic infection in 75%-80% of cases; other 20% appear to mount successful immunologic response and eliminate viral RNA.
• Chronic infection associated with chronic hepatitis and cirrhosis in many patients
• However the frequency of severe liver disease and death is controversial
• In USA about 50% of hepatocellular carcinoma cases are infected with HCV
Treatment of Chronic HCV

- Indications: evidence of progressive disease (fibrosis on liver biopsy, elevated ALT/AST)
- Check HCV RNA level and viral genotype prior to treatment (genotype influences treatment success)
- Rx: Interferon alpha 3 million units three times weekly plus ribavirin continued for 24 to 48 weeks
- Monitor treatment success by HCV RNA levels
- Sustained response (undetectable HCV RNA at one year post RX) in 50% or less of patients
HCV: Blood Safety

• **Donor Exclusions**: injection drug users and those with recent parenteral risks

• **Blood Testing**:
  – 3rd generation HCV antibody tests by enzyme immunoassay (EIA)
  – Recombinant immunoblot (RIBA) supplemental test
  – Nucleic acid testing (NAT) in developed countries due to long “window period” from infection to positive antibody result
HCV vaccine.....not yet available

• Until recently, lack of in-vitro culture system; primate studies difficult.
• Lack of effective immune response in most naturally infected humans.
• Current research directed at understanding immunology and genetics in 20% of humans who resolve infection naturally.
Human immunodeficiency virus (HIV) Epidemiology

• Blood donor prevalence ranges from 1 per 10,000 (developed countries) to 5-10 percent (sub-Saharan Africa)

• Prevalence highest in sexually-active 15-40 year olds, who are also most likely to donate blood

• 10 year incubation period leads to large pool of asymptomatic carriers and ongoing transmission

• Prevention and treatment of HIV infection are mainstays of public health response
HIV Natural history. HIV RNA levels rise quickly about 10 days after infection coincident with febrile syndromes in some patients, then decline slightly but remain detectable at different levels in each patient. P24 antigen follows the same course at lower levels. HIV antibody is detectable after about 21 days by current sensitive enzyme immunoassay and western blot assays. HIV infection is always chronic, with persistence of RNA and antibody, although rare patients may show no decline in CD4 lymphocyte count nor clinical symptoms.
HIV: Clinical

- Acute infection syndrome = self-limited fever, malaise and lymphadenopathy soon after HIV infection.
- Gradual decline of CD4+ lymphocyte counts over years since infection; HIV viral load varies between individuals.
- Patients may become symptomatic as CD4+ count declines below 350.
- Acquired Immunodeficiency Syndrome (AIDS) defined by CD4+ count < 200 or diagnosis of AIDS-defining disease.
## HIV: Starting Antiretroviral Treatment

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4⁺ T Cell Count</th>
<th>Plasma HIV RNA</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic (AIDS, severe symptoms)</td>
<td>Any value</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic, AIDS</td>
<td>&lt;200 cells/μL</td>
<td>Any value</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;200 cells/μL but &lt;350 cells/μL</td>
<td>Any value</td>
<td>Treatment should be offered, with consideration of pros and cons</td>
</tr>
</tbody>
</table>

# HIV: Treatment (2)

<table>
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<th>CD4⁺ T Cell Count</th>
<th>Plasma HIV RNA</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>&gt;350 cells/µL</td>
<td>≥100,000 copies/mL</td>
<td>Most clinicians recommend deferring therapy; some will treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>&gt;350 cells/µL</td>
<td>&lt;100,000 copies/mL</td>
<td>Defer therapy</td>
</tr>
</tbody>
</table>

http://www.aidsinfo.nih.gov/guidelines/
HIV: Blood Safety

- **Donor Exclusions**: sexual promiscuity, injection drug use, other high risk groups
- **Blood Testing**:
  - Antibody testing by with sensitive enzyme immunoassay (EIA) containing recombinant HIV peptide antigens.
  - Supplemental testing with Western blot before counseling EIA positive blood donors
  - Nucleic acid testing (NAT) for HIV RNA in developed countries (expensive)
  - HIV antibody/antigen combination tests more cost-effective for developing countries
Advantages and Limitations of Blood Testing

• Antibody testing of blood donors for HBV, HCV and HIV is especially cost effective in developing countries because of higher prevalence of these infections.
• However antibody tests may be false-negative in early infection (“window period”) before antibody titers rise.
• Nucleic acid testing (NAT) can detect “window period” infections, but is expensive and technically demanding.
• Antibody/antigen combination tests are slightly less sensitive than NAT but more affordable.
Advantages and Limitations of Blood Testing

THEREFORE........

• Recruitment of volunteer blood donors and exclusion of those with risk factors is essential to reduce prevalence, and thereby lower chance of false-negative laboratory screening.
The Pre-Donation Screening Controversy

Definition: Lab testing, often with a rapid test, of prospective donors before allowing them to donate a unit of blood.

Pro: In very high prevalence areas (e.g. HBV or HIV in sub-Saharan Africa) as many as 10 percent of blood units are discarded for positive tests; pre-testing reduces waste of expensive plastic collection bags.

Con: WHO discourages pre-donation testing as counter-productive to establishing a safe, volunteer donor program.
Rational Transfusion Therapy

The best way to minimize TTID is to avoid unnecessary transfusions:

- Establish transfusion guidelines in collaboration with clinical specialties (esp. surgery and OB/GYN)
- Use “transfusion trigger” of Hemoglobin <8 gm rather than <10 gm
- In patients without concurrent cardiopulmonary disease, base transfusion on symptoms of anemia, not lab value
- Use of iron supplementation after acute blood loss
National Blood Plans

WHO recommends that implementation of Safe Blood Programs requires action at the national level:

- Legislation to establish regulation
- Development of blood safety Standards
- Consolidation/closure of small blood banks in favor of larger, more efficient regional blood centers
- Development of information systems for record-keeping and quality control

Summary

- Recruitment of volunteer blood donors and the exclusion of those with risk factors is the keystone of blood safety.
- Current antibody tests for HBV, HCV and HIV provide an additional, cost-effective safety measure.
- Establishment of National Blood Plans and transfusion guidelines provide the necessary institutional framework.
Credits

Edward L. Murphy, MD, MPH
Professor, University of California San Francisco
Senior Investigator, Blood Systems Research Institute
San Francisco, California, USA
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