CHAPTER 7  Infectious Disease Screening

An alternative method of protecting the blood supply from infectious agents is pathogen inactivation. Heat-inactivation, solvent/detergent (SD) treatment, nanofiltration, chromatography, cold ethanol fractionation, and other approaches have been used with remarkable success to inactivate or remove residual pathogens in plasma derivatives. Pathogen inactivation systems for platelets and transfusable plasma have been available outside the United States for several years, and one manufacturer’s system was FDA approved for use in the United States in December 2015 (INTERCEPT Blood System, Cerus Corp., Concord, CA). SD-treated plasma (SD plasma) is also available for transfusion in the United States; Octaplas (Octapharma, Lachen, Switzerland) is manufactured from pools of human source plasma (630-1520 individual donors). Pathogen inactivation systems are discussed later in this chapter.

The AABB Transfusion-Transmitted Diseases Committee published an extensive review of infectious agents that are possible threats to the blood supply. Potential mitigation strategies were discussed for each agent, including the documented or theoretical efficacy of pathogen inactivation processes. AABB periodically updates this information via its website, adding materials for new potential threats as they are identified. The agents deemed to pose the highest threat from either a scientific or public perspective are briefly discussed in this chapter. (See the 2009 supplement to TRANSFUSION and updates on the AABB website for a more thorough review of these potential infectious risks.)

SCREENING FOR SPECIFIC AGENTS

Human Immunodeficiency Virus

HIV-1, a lipid-enveloped, single-stranded RNA spherical retrovirus containing two linear, positive-sense strands of RNA, was identified in 1984 as the causative agent of AIDS. Blood donation screening for antibodies to this virus was implemented in the United States in 1985. In 1992, donor screening tests were modified to include detection of antibodies to HIV-2, a closely related virus identified initially in West Africa, only rarely identified in the United States.

HIV can be transmitted sexually, parenterally, and from infected mothers to their infants. Although heterosexual and vertical spread of HIV predominate in some parts of the world, new HIV cases in the United States continue to be concentrated in men who have sex with men (MSM) and individuals with high-risk heterosexual contact (defined as contact with an individual who is HIV positive.

### TABLE 7-6. Estimated Risks of Transfusion-Transmitted Infection in the United States Based on the Incidence/Window-Period Model*

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Agent</th>
<th>Incidence per $10^5$ Person/Years</th>
<th>Infectious Window Period (days)</th>
<th>Residual Risk per Donated Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007-2008§*</td>
<td>HIV</td>
<td>3.1</td>
<td>9.1</td>
<td>1:1,467,000</td>
</tr>
<tr>
<td>2007-2008§*</td>
<td>HCV</td>
<td>5.1</td>
<td>7.4</td>
<td>1:1,149,000</td>
</tr>
<tr>
<td>2009-2011§†</td>
<td>HBV</td>
<td>1.6</td>
<td>26.5-18.5</td>
<td>1:843,000 to 1:1,208,000</td>
</tr>
</tbody>
</table>

*HIV and HCV risk estimates are based on minipool nucleic acid testing in pools of 16.
*HBV risk estimates are based on minipool nucleic acid testing in pools of 16 using the Grifols Ultrio Plus assay. The range indicated for the HBV window period reflects uncertainty regarding the minimum infectious dose of HBV (1 copy in 20 mL plasma vs 10 copies in 20 mL).

HIV = human immunodeficiency virus; HCV = hepatitis C virus; HBV = hepatitis B virus.
or in an identified risk group for HIV, such as MSM or injection drug users). Current donation screening for HIV includes NAT for HIV-1 RNA and serologic testing for antibodies to HIV. The antibody tests approved for donor screening detect both immunoglobulin M (IgM) and IgG antibody to both HIV-1 and HIV-2. Current-generation assays also detect antibody to HIV-1 group O, a strain of HIV-1 found primarily in Central and West Africa. With this detection claim, donor centers no longer need to exclude individuals who have resided in, received medical treatment in, or had sex partners from HIV-1 group O endemic areas.

The average window period after HIV-1 infection to test detection is currently estimated to be 9.0 to 9.1 days for MP-NAT. Based on window-period and incidence-rate calculations, the current risk in the US of acquiring HIV from transfusion is estimated to be approximately 1 in 1.5 million units (Table 7-6). In the United States, blood donor screening questions exclude very broadly defined populations at increased risk of HIV. Given the short delay of only days between infection and detection of infection by NAT, experts have questioned whether donor interviews and exclusion of donors with increased risk remain medically necessary. The continued importance of a low-risk donor population becomes evident if different HIV incidence figures are used for the blood safety calculation. For example, HIV incidence rates as high as 1% to 8% have been observed in some high-risk populations, such as young urban MSM. If an individual from a population with a 1% incidence of HIV donates blood, the likelihood that this individual is in the window period and that the component will transmit HIV can be calculated as follows:

\[
\text{Risk that the donation is in window period} = \frac{\text{length of window period} \times \text{incidence of infection in donor population}}{\text{year}} = \frac{9.0 \text{ days}}{365 \text{ days/year}} \times \frac{1}{100 \text{ person-years}} = \frac{1}{4100}.
\]

This is the likelihood that a unit from this high-risk donor would harbor HIV but be missed by the current donor screening. This risk is clearly much higher than the estimated HIV transmission risk of 1 in 1.5 million for a unit of blood obtained from the current donor population. Thus, despite the short window period with current testing, inclusion of donors with a high risk of HIV would have a profoundly adverse impact on blood safety. Accordingly, questioning of donors for risk and temporarily excluding those at increased risk to minimize window-period donations continue to be critical for preserving blood safety.

Although there has been great interest in developing a more specific donor-screening algorithm for MSM that would exclude only individuals who are truly at increased risk of HIV, the FDA guidance issued in December 2015 indicates that the efficacy of a more specific algorithm has not yet been established. This guidance lists the current definitions of potential risks for HIV exposure in the United States that require donor deferral. Most of these risk categories, including MSM behavior, now require a 12-month deferral.

**Hepatitis B Virus**

HBV is a lipid-enveloped, spherical virus in the *Hepadnaviridae* family. It is unique in that it has a partially double-stranded circular DNA genome with overlapping reading frames. Like HIV, HBV is transmitted parenterally, sexually, and perinatally. Jaundice is noted in only 25% to 40% of adult cases and in a smaller proportion of childhood cases. A large percentage of perinatally acquired cases result in chronic infection, but most HBV infections acquired in adulthood are cleared. HBV is highly prevalent in certain parts of the world, such as eastern Asia and Africa, where perinatal transmission and resultant chronic infection have amplified infection rates in the population. In the United States, the incidence of acute HBV infection has decreased by at least 80% with the implementation of routine vaccination programs. Perinatal screening and newborn prophylaxis have also been effective in reducing perinatal transmission.

During HBV infection, DNA and viral envelope material (HBsAg) are typically detectable in circulating blood. Antibody to the core
antigen is produced soon after the appearance of HBsAg, initially in the form of IgM antibody, followed by IgG. As infected individuals produce antibody to the surface antigen (anti-HBsAg), the HBsAg is cleared.

The FDA requires donor screening for HBsAg, HBV DNA, and total anti-HBc (IgM and IgG antibody). Measurements of HBV incidence in donors have been complicated by the transience of HBsAg and false-positive results on the HBsAg test. Published estimates of the infectious window have varied because of differences in the sensitivity of various HBV assays and lack of certainty regarding the level of virus in a blood component that is required for infectivity. Recent publications provide window-period estimates for different potential infectious doses of virus (eg, 10 copies/20 mL of plasma vs 1 copy/20 mL of plasma). The infectious window before a positive result on the Abbott PRISM (Abbott Laboratories, Abbott Park, IL) HBsAg test has been estimated to be 30 to 38 days. With the addition of HBV DNA testing in MPs of 16, the window period is estimated to have been reduced to 18.5 to 26.5 days. Using these MP testing estimates, US HBV transfusion-transmission risk has been estimated to be between 1 in 843,000 donations and 1 in 1.2 million donations (Table 7-6). Donor screening for HBV DNA can be of value at a variety of points in infection. HBV DNA may be detected during the infectious window period before HBsAg detection; however, DNA levels may be low and could be below the limits of detection of MP-NAT assays. Later in infection, following the clearance of HBsAg, HBV NAT may detect persistent (ie, “occult” HBV) infection. Such infections are interdicted in the United States by the donor screening test for anti-HBc, with about 1% of anti-HBc repeat-reactive donations considered to be from donors with occult HBV infection due to the presence of HBV DNA in the absence of detectable HBsAg. High sensitivity NAT is required to detect occult HBV infections because viral loads are typically low. HBV NAT can also detect acute HBV infections in individuals who have previ-ously been vaccinated. Such individuals may never develop detectable HBsAg, but they may have detectable DNA. The infectivity of such donations is not known because these units contain vaccine-induced antibodies to HBsAg in addition to the virus. Routine HBV DNA screening of US blood donations detects at least some of these infections.

**Hepatitis C Virus**

HCV is a small lipid-enveloped, single-stranded RNA virus in the family *Flaviviridae*. HCV was shown to be the cause of up to 90% of cases previously called NANB transfusion-related hepatitis. The majority of HCV infections are asymptomatic. However, HCV infection is associated with a high risk of chronicity, which can result in liver cirrhosis, hepatocellular carcinoma, and a variety of extrahepatic syndromes.

HCV is thought to be transmitted primarily through blood exposure. In the United States, about 55% of HCV infections are associated with injection drug use or receipt of transfusion before donor screening in 1992, but the risk factors for the remainder of the infections are not clear. Sexual and vertical transmissions are uncommon, although co-infection with HIV increases transmission rates by these routes.

Current donor screening for HCV includes testing for HCV RNA and serologic testing for antibodies to HCV. The average window period between exposure and detection of infection by MP-NAT is estimated to be 7.4 days. The serologic test detects only IgG antibody, a relatively late marker of infection. Therefore, there may be a significant lag (1.5 to 2 months) between detection of RNA and detection of antibody. Donor questioning has limited potential to exclude individuals who may be harboring HCV infection because a large proportion of infected individuals are asymptomatic and admit to no risk factors or possible exposure. Despite this limitation, the current estimated US risk of HCV transmission by transfusion is extremely low—approximately 1 in 1.1 million (Table 7-6).