Preventing transmission of infectious diseases through blood transfusion presents one of the greatest challenges of transfusion medicine. The emergence of acquired immunodeficiency syndrome (AIDS) in the 1980’s heightened public awareness of the complications of transfusion, and for the first time, many patients and clinicians became concerned with the specifics of blood collection and testing. Although the risk is lower than ever before, the risk of transmitting viral, bacterial, and parasitic diseases through transfusion persists, along with the potential for novel infectious agents. Several recent textbooks and reviews address these issues.

Hepatitis

Hepatitis is inflammation of the liver that can be caused by many different toxic and infectious agents, including hepatitis A, B, C, D, and E viruses (HAV, HBV, HCV, HDV, HEV), as well as cytomegalovirus (CMV), Epstein-Barr virus (EBV), and others. Infectious agents that pose a serious threat to transfusion recipients are those that persist in the circulation of asymptomatic individuals who are healthy enough to be blood donors.

Several viruses, such as HAV, circulate only transiently during the initial acute phase of infection, when the individual is clinically ill and not a candidate for donation, and generally they are not a serious threat to transfusion recipients. However, viremia may be present for up to 28 days before symptoms develop; blood donated during this viremic phase could be infective, but only a few documented transfusion-transmitted cases have been reported.

Although HDV, formerly called the delta agent, can cause infection after transfusion or other parenteral transmission, it causes disease only when there is concomitant or prior HBV infection. HEV causes an epidemic enteric form of hepatitis, but there have been no reports of spread by transfusion. The agent of a transfusion-associated and community-acquired non-A, non-B, non-
C hepatitis has been cloned and shown to be a novel flavivirus distinct from HCV.

Clinical Manifestations of Hepatitis

Most individuals who acquire HBV or HCV infection have a subclinical infection without obvious symptoms or physical evidence of disease. Some develop overt hepatitis with jaundice, nausea, vomiting, abdominal discomfort, fatigue, dark urine, and elevation of liver enzymes. Signs and symptoms usually resolve spontaneously. Hepatitis C tends to be milder than hepatitis B, but in either hepatitis B or C, the clinical course of infection may be complicated by fulminant hepatitis, relapsing or chronic hepatitis, or long-term progression through cirrhosis to hepatocellular carcinoma. Hepatitis A tends to be quite mild, clinically, and virtually never progresses to chronic hepatitis or a chronic carrier state.

Chronic Carriers of HBV

After initial HBV or HCV infection, some patients fail to clear infectious material from the bloodstream and become chronic carriers for years or even for life. HBV carriers produce, in addition to the infectious viral particle, large amounts of noninfectious material detected by the assay for hepatitis B surface antigen (HBsAg). About 5% of those infected with HBV as adults become HBsAg carriers; the vast majority recover and develop protective antibody against HBsAg (anti-HBs). The risk of becoming an HBsAg carrier is strongly age-dependent; 90% or more of infants infected perinatally become carriers, and many progress to cirrhosis and cancer. There are approximately 300 million HBsAg carriers worldwide with a prevalence of up to 10% in some Asian countries, 0.1-0.5% in the United States, and 0.02-0.04% in US blood donors.

Chronic Carriers of HCV

Most persons infected with HCV become chronic carriers, with 70-80% having persistent infection as demonstrated by HCV RNA in serum and liver; at least 50% of these have biochemical or histologic evidence of chronic liver disease. Despite this chronic inflammatory process, most HCV-infected individuals remain asymptomatic. Whereas the acute infection with HCV is clinically benign, approximately 10% of patients with chronic HCV infection develop cirrhosis and/or hepatocellular carcinoma decades after the acute event.

Posttransfusion Hepatitis

The risk of posttransfusion HBV has fallen dramatically, from an estimated 1 in 10 a decade ago to an estimated 1 in 50,000 transfused recipients or about 1 per 200,000 transfused units. HCV antibody testing combined with stringent selection measures for donors have contributed to this remarkable decline. After implementation of the first generation of anti-HCV tests, the risk was estimated at one case per 3300 units transfused. With presently available, more sensitive tests, the risk is probably lower, but is difficult to determine because posttransfusion hepatitis is often asymptomatic.

Hepatitis A Virus

Because HAV infection does not cause a chronic carrier state, transmission by blood transfusion requires the collection of blood from a viremic donor, usually late in the incubation phase just before signs or symptoms occur. Several of the rare transfusion-transmitted HAV infections occurred in infants, making secondary transmission by fecal-oral spread more frequent than would be expected from adults who sustain the usually mild disease. In 1991 and 1992, an
outbreak of hepatitis A infection occurred in several European hemophilia centers, associated with Factor VIII concentrate manufactured in two plants by a single manufacturer, but such an outbreak has not been reported in the United States. ^HAV, which lacks a lipid envelope, is not inactivated by solvent/detergent treatment.

**Serologic Markers**

Laboratory tests can identify markers of previous exposure and probable current infectivity for HBV and HCV. Table 26-1 lists the serologic tests commonly used in the diagnosis of hepatitis and includes terms and abbreviations in current use.

![Yield of targeted lookback](Image)

Figure 26-1. The decline in posttransfusion HCV infection (reprinted with permission from Busch MP, et al).
### Table 26-1. Serologic Tests in the Diagnosis of Viral Hepatitis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Test Reactivity</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B Virus</strong></td>
<td>HBsAg</td>
<td>Anti-HBc</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>IgM</td>
</tr>
<tr>
<td>+</td>
<td>+/–</td>
<td>+/–</td>
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<td>+</td>
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<td>–</td>
</tr>
<tr>
<td><strong>D Virus</strong></td>
<td>HBsAg</td>
<td>Anti-HBc</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>A Virus</strong></td>
<td>Anti-HAV</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>IgM</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>Acute HAV</td>
</tr>
<tr>
<td>+</td>
<td>–</td>
<td>Recovered HAV or vaccinated</td>
</tr>
</tbody>
</table>
### C Virus Anti-HCV Recombinant Antigens

<table>
<thead>
<tr>
<th>C Virus Anti-HCV (Screen)</th>
<th>Recombinant Antigens</th>
<th>C-100-3</th>
<th>5-1-1</th>
<th>C22-3</th>
<th>C33-c</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>Not Available</td>
<td>+/-</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>+</td>
<td>+</td>
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</table>

Possible acute or chronic HCV
Probable chronic HCV
Probable false positive
Probable chronic HCV
False positive or acute or chronic HCV
False positive or acute or chronic HCV
False positive

### E Virus Anti-HEV

<table>
<thead>
<tr>
<th>E Virus Anti-HEV</th>
<th>Total IgM</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Acute HEV
Recovered HEV

Abbreviations used include: HBsAg (hepatitis B surface antigen), anti-HBc (antibody to hepatitis B core antigen), anti-HBs (antibody to HBsAg), HBeAg (hepatitis B e antigen), anti-HBe (antibody to HBeAg), anti-delta (antibody to delta antigen), anti-HAV (antibody to hepatitis A virus), anti-HCV (antibody to hepatitis C virus) and anti-HEV (antibody to hepatitis E virus).

*Those with HBeAg are more infectious and likely to transmit vertically.
antigen is usually present in great excess relative to the concentration of infectious virus.

Anti-HCV has been detected in 80-90% of samples from patients initially diagnosed as having non-A, non-B (NANB) hepatitis, either transfusion- or community-acquired. Tests for antibodies to HCV are enzyme immunoassays (EIA) using recombinant antigens of HCV coated on a solid phase as the capture reagent. Figure 26-3 shows the proposed structure of the genome of HCV and the specific gene products incorporated in test kits for anti-HCV.

The clinical significance of a positive screening test for anti-HCV in healthy blood donors is unclear without supplemental testing. Between 0.4 and 1.0% of US blood donors have repeatedly reactive EIA results. Some of these individuals have asymptomatic chronic HCV infection, and their blood is potentially infective; others may have false-positive results. A recombinant immunoblot assay (RIBA) has been licensed by the Food and Drug Administration (FDA) for further differentiation of repeatedly reactive EIA results. An individual who is positive by RIBA is considered to have true anti-HCV antibody; in these cases, HCV nucleic acid is almost always detectable by polymerase chain reaction (PCR) and infectivity rates of 80-90% have been reported. Regardless of RIBA results, a donation with a repeatedly reactive EIA result cannot be used for transfusion.

**Surrogate Markers**

Before HCV was identified and anti-HCV testing feasible, several tests on donor blood were introduced to reduce NANB hepatitis following transfusion. In the absence of specific tests for the NANB agent, the AABB in 1987 mandated testing for alanine aminotransferase (ALT) and anti-HBc, as surrogates for the direct detection of the agent. Posttransfusion hepatitis declined thereafter, but the impact of surrogate testing on the
safety of transfusion has been difficult to evaluate. More stringent criteria for donor selection had recently been introduced in response to reports of AIDS in transfusion recipients. Because some of the populations at risk for HIV infection also have high risk for NANB and HBV infection, the changes in donor eligibility criteria may have affected hepatitis transmission.

One study during this period observed a drop in the incidence of hepatitis in the general population, but there were much greater drops in posttransfusion HBV and NANB infection than could be explained simply by the change in background rates.

Current very sensitive tests for anti-HCV have deprived surrogate tests of their role in preventing NANB hepatitis. A National Institutes of Health (NIH) consensus conference held in 1995 recommended that screening of volunteer blood donors for ALT be discontinued but considered testing for anti-HBc to have a continued role in preventing HBV transmission. AABB Standards no longer requires ALT testing and allows reentry of otherwise suitable donors who had previously been excluded solely because of elevated ALT.

**Human Immunodeficiency Virus**

Human immunodeficiency virus, type 1 (HIV-1) is the etiologic agent of AIDS. This syndrome was recognized in 1981, well before the discovery of the causative virus. Wider implications of the immune disorder were noted when, in 1982, AIDS was reported in three hemophiliacs and in a 17-month-old infant whose multiple transfusions at birth included a unit of platelets from a donor who subsequently developed AIDS. Within a few years, over 50% of hemophiliacs receiving clot-
ting factor concentrates developed HIV-1 infection.

Properties of the Virus

Montagnier and Gallo identified HIV as the viral cause of AIDS. HIV is a cytopathic retrovirus initially called lymphadenopathy-associated virus (LAV) or human T-cell lymphotropic virus, type III (HTLV-III). It is a 100 nm RNA virus that preferentially infects CD4-positive T lymphocytes (helper cells) in lymph nodes and other lymphoid tissue, but also infects other cells that express CD4. The core of the retrovirus contains an enzyme, reverse transcriptase, that enables the virus to copy its single-stranded RNA into DNA; the viral DNA is then integrated into host DNA. Viral replication and release are complex processes requiring the products of several viral genes.

HIV virus then replicates and disseminates initially as cell-free virions, and a few weeks after infection, viremia is first detectable in the plasma. During this viremia, 20-50% of acutely infected persons have a mononucleosis-like illness, with fever, enlarged lymph nodes, sore throat, rash, joint and muscle pain with or without headache, diarrhea, and vomiting.

As HIV-1 antibodies appear and symptoms resolve, viremia diminishes, leaving some infected peripheral blood T lymphocytes. The virus can be transmitted by blood or genital secretions during this phase. Tissue monocytes may serve as a latent infected reservoir in nonlymphoid tissues.

Persistent infection of CD4+ T lymphocytes with an asymptomatic clinical status has been observed to last a median of 10 to 12 years. (See Fig 26-4.) After years of asymptomatic standoff, both viremia and the percentage of infected T lymphocytes increase. Loss of the immune functions served by helper T cells impairs immune reactivity, and there

Figure 26-4. Natural history of HIV infection and its serologic markers.
may be inappropriate immune activation and cytokine secretion. Eventually there is a sharp decline in the number of viable CD4+ T lymphocytes and profound immunosuppression.

**Definition of AIDS**

As the number of CD4+ cells decreases, the risk and severity of opportunistic illnesses increase. Enumeration of CD4+ cells is used to guide clinical and therapeutic management of HIV-infected persons. The AIDS classification system devised by the CDC evaluates the number of CD4+ T cells (≥500/µL, 200-499/µL, or ≤ 200/µL), the presence or absence of systemic symptoms, and existence of any of the 26 clinical conditions considered to be AIDS-defining illnesses. Among these conditions are Kaposi’s sarcoma; cytomegalovirus retinitis, or infection of sites other than liver, spleen, or lymph nodes; toxoplasmosis of the brain; primary lymphoma of the brain; candidiasis of the esophagus, bronchi, trachea or lungs; tuberculosis at any site or infection with atypical mycobacteria; and chronic intestinal cryptosporidiosis. *Pneumocystis carinii* pneumonia (PCP) is the most common serious opportunistic infection.

**Risk Factors for HIV Infection**

Infected individuals are at risk of infecting others through sexual contact, childbirth, breast-feeding, and parenteral exposure to blood. Those identified early as being at highest risk were men who had sex with other men; needle-sharing drug users; hemophiliacs who received clotting factor concentrates; and, to a lesser extent, recipients of blood transfusions. By 1989 the rate of infections spread within each group was no longer increasing exponentially and appeared to have reached a plateau in the populations most at risk, and HIV seroprevalence had stabilized in most US cities. Heterosexual transmission, especially male-to-female, and mother-to-child transmission have attracted increasing concern.

**Human Immunodeficiency Virus, Type 2**

First discovered in 1985, human immunodeficiency virus, type 2 (HIV-2) causes endemic infection in many countries in West Africa but is seldom seen elsewhere. The first case of HIV-2 infection in the United States was reported in March 1988 in a young West African who had recently immigrated to the United States. The spectrum of disease attributable to HIV-2 is similar to that caused by HIV-1; however, there appears to be a longer incubation period and lower incidence of progression to AIDS. HIV-2 is spread both sexually and vertically, but transmission is less efficient than for HIV-1. Tests in the United States on injecting drug users, persons with sexually transmitted diseases, newborn infants, and homosexual men confirm the very limited prevalence and transmission of the agent.

**Transfusion Considerations**

**Transfusion-Transmitted HIV-1**

All blood components can transmit HIV-1. By the mid-1990’s over 7500 cases of AIDS had been reported in which transfusion or a tissue transplant was the only identifiable risk. In addition, approximately 4200 cases occurred in hemophiliacs who received clotting factor concentrates. Transfusion-associated AIDS, including cases in hemophiliacs, constituted about 2.3% of all AIDS cases. All but about 30 reflected transfusions given before routine anti-HIV testing began, in 1985. The interval between transfusion and diagnosis of AIDS was a median of 58 months.
Most but not all recipients of HIV-infected blood transfusions become infected. In one large study, HIV infection developed in 89.5% of recipients who received blood from anti-HIV positive donors. With the exception of coagulation factor concentrates, plasma derivaties such as albumin and immune globulins have not been reported to transmit HIV infection.

Transfusion-Transmitted HIV-2

There have been two brief reports of possible HIV-2 transmission through blood component use, both in Europe. Two women were infected by whole blood obtained from a donor who developed AIDS at least 16 years after becoming infected with HIV-2; both women were asymptomatic 14 years after transfusion. Two hemophiliac patients who received clotting factors were also infected.

Risk of Posttransfusion HIV

Since 1985, the cases of HIV transmission by transfusion have resulted from donation by a recently infected individual not yet reactive on an anti-HIV screening test. With screening tests available before 1992, the seronegative interval (“window period”) averaged 45 days. Presently available, more sensitive screening tests now have closed the seronegative window to approximately 22-25 days.

Since implementing donor testing to prevent posttransfusion HIV infection in 1985, the risk of transfusion-transmitted HIV has declined remarkably (Fig 26-5). In the San Francisco area, the peak risk of transmitting HIV between 1978 and 1985, was almost 1% per unit. Donor screening policies in 1983 and 1984 lowered the transmission risk substantially and the introduction of testing for anti-HIV accelerated the rate of decline. Since 1985, the sensitivity of antibody detection has continued to improve.

Figure 26-5. Projected risk of HIV-1 infection per unit of blood transfused between January 1978 and December 1984 (reprinted with permission from Busch MP, et al 11).
Risk from seronegative donations will vary in proportion to the incidence of HIV infection in the donor community. Recent overall estimates of posttransfusion HIV risk in the United States approximate one per 420,000 transfusions. 2,41

**HIV Testing of Blood Donors**

AABB Standards and the FDA require that all units of blood and components be nonreactive for anti-HIV-1 and HIV-2 and for HIV-1 antigen (HIV-1-Ag) before they are issued for transfusion.

**Screening Tests for Antibodies to HIV-1/2**

Figure 26-6 shows the sequence of screening and confirmatory testing for anti-HIV-1/2. EIA is the test of choice of most donor centers for donor screening. Because the consequence of missing even one true positive is great, screening tests are designed to have high sensitivity, calculated as True Positive/(True Positive + False Negative) × 100. Specificity, calculated as True Negative/(True Negative + False Positive) × 100, is much less significant. Current tests for anti-HIV have specificity in excess of 99.5%. Specificity indicates the accuracy of findings in tested persons who do not have the disease. If the disease has low prevalence in the test population, the likelihood is high that most positive screening test results will be false positive.

EIA-detectable antibody develops days to a week after the onset of symptoms, about 6 days after the onset of HIV p24 antigenemia. A few days later HIV-1 antibodies become detectable by the HIV-1 Western immunoblot.

**Confirmatory Testing for Antibodies to HIV-1/2**

The most commonly used confirmatory test for antibodies to HIV-1/2 is the
Western blot (WB). With this technique, protein components (in this instance, antigenic viral material) are separated into bands according to molecular weight and transferred to a nitrocellulose membrane. Antibody(ies) in the test serum react with individual bands, depending on the specificity(ies) present. Most persons infected with HIV, whether asymptomatic or exhibiting AIDS, show multiple bands, representing antibodies to essentially all of the various gene products. A fully reactive test serum should react with the p17, p24, p26, and p55 gag proteins; the p31, p56, and p66 pol proteins; and the gp41, gp120, and gp160 env glycoproteins.

A sample is defined as anti-HIV-positive if at least two of the following bands are present: p24, gp41, or gp120/160. Negative WB results have no bands present. WB results classed as indeterminate have some bands present but not those in the criterion for HIV positivity. Individuals infected with HIV may have indeterminate WB patterns when initially tested, but develop additional bands within 6 months. Healthy individuals with an initial indeterminate WB continue to have indeterminate results on repeat samples, and are negative on clinical examination and additional tests, including viral cultures and PCR. Healthy donors who continue to show the same indeterminate pattern for more than 6 months can be reassured that they are unlikely to have HIV infection, but they are not eligible to donate blood.

**Confirmation and Reentry, Anti-HIV-1/2**

When the EIA screening test for anti-HIV-1 is repeatedly reactive, a confirmatory test will determine whether the donor is a true positive and will aid in counseling the individual. Persons who have true positive test results should be notified confidentially and encouraged to obtain counseling and medical follow-up. EIA anti-HIV-1/2 results not confirmed as a true positive may have technical or biologic causes. Many blood donors with repeat-reactive EIA anti-HIV-1/2 screening tests are negative on WB confirmatory testing; these donors usually have nonreactive EIA results on a subsequent donation. Therefore, the FDA has approved reentry protocols to qualify donors as suitable for subsequent donations (see Table 26-2). Reentry requires retesting at least 6 months later, to detect delayed seroconversion; the use of EIA tests based on whole-virus lysate; and use of either a licensed Western blot to ensure appropriate sensitivity of the methods or an FDA-licensed immunofluorescence assay. The later sample must also be nonreactive in an EIA test for anti-HIV-2, if standard testing does not include HIV-2, and a test for HIV-1-Ag.

**Direct Detection of Virus**

AABB [Standards] and the FDA require that all units of blood and blood components be nonreactive for an FDA-licensed test for HIV-1-Ag. HIV-1-Ag may appear in blood early in the course of infection, somewhat before antibody is detectable. Transmission of HIV has been reported from transfusion of seronegative blood later shown to contain p24 antigen; the donors subsequently seroconverted. Mathematical models, constructed with findings from geographic areas with very high incidence of new HIV infections, suggest that routine antigen testing would detect one antigen-positive/antibody-negative donation in every 1.6 million tested.

**Confirmatory Testing for HIV-1 Antigen**

When the EIA screening test for HIV-1-Ag is repeatedly reactive, a confirmatory test will aid in counseling the donor. The
Table 26-2. Reentry of Donors With Repeatedly Reactive Screening Tests

<table>
<thead>
<tr>
<th>Tests</th>
<th>Anti-HIV-1 or -HIV-1/2</th>
<th>Anti-HIV-2</th>
<th>HIV-1-Ag</th>
<th>HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial sample</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not eligible for reentry</td>
<td>Licensed Western blot positive or indeterminate or IFA reactive</td>
<td>Different HIV-2 EIA RR</td>
<td>Confirmed by neutralization</td>
<td>Confirmed by neutralization or anti-HBc RR</td>
</tr>
<tr>
<td>Evaluate for reentry</td>
<td>Licensed Western blot or IFA NR</td>
<td>Different HIV-2-EIA NR and licensed Western blot or IFA NR</td>
<td>Not confirmed by neutralization</td>
<td>Not confirmed HBsAg specific and anti-HBc NR</td>
</tr>
<tr>
<td><strong>Follow-up sample</strong></td>
<td>(drawn 6 months later)</td>
<td>(drawn 6 months later)</td>
<td>(drawn 8 weeks later)</td>
<td>(drawn 8 weeks later)</td>
</tr>
<tr>
<td>Not eligible for reentry</td>
<td>EIA RR or Western blot positive or indeterminate or IFA reactive</td>
<td>HIV-1-Ag RR, neutralization confirmed</td>
<td>HBsAg RR or anti-HBc RR</td>
<td></td>
</tr>
<tr>
<td>Eligible for reentry</td>
<td>Original EIA method NR and whole virus lysate anti-HIV-1 EIA NR and licensed Western blot or IFA NR</td>
<td>Screening test and a different HIV-2 EIA NR and licensed Western blot or IFA NR</td>
<td>HIV-1-Ag and anti-HIV-1/2 NR or HIV-1-Ag RR, not confirmed (temporary deferral for 8 weeks)</td>
<td>HBsAg NR and anti-HBc NR</td>
</tr>
</tbody>
</table>

NR = nonreactive
RR = repeatedly reactive
confirmatory test is an EIA neutralization test. Donors whose serum shows neutralization with this test are considered confirmed positive for HIV-1-Ag and should be permanently deferred. Donors whose serum shows no neutralization with this test are currently considered not confirmed, and must be reported as HIV-1-Ag indeterminate; they should be temporarily deferred from donation for a minimum of 8 weeks. See below for the reentry protocol for HIV-1-Ag. Units from repeatedly reactive donations must be quarantined, destroyed or not used for transfusion or for further manufacturing into injectable products. Units from repeatedly reactive autologous donations should be withheld from transfusion. However, these units may be supplied for autologous use only if: 1) there is a written, signed, and dated request from the patient’s physician authorizing this shipment, 2) there is a written statement from the transfusion service indicating willingness to receive this product, and 3) the transfusion service takes responsibility for ensuring that there is documented verification of the accurate identity of the transfusion recipient. These units must be labeled “BIOHAZARD” and “FOR AUTOLOGOUS USE ONLY.”

In the absence of a repeatedly reactive anti-HIV-1/2 test, a repeatedly reactive EIA HIV-1-Ag screening test should be further tested with a neutralization test for the purposes of counseling. Persons with a confirmed HIV-1-Ag test should be notified confidentially and encouraged to obtain counseling and medical follow-up. These persons should be informed that they are probably infected.

Figure 26-7. Virologic events during primary HIV infection. After initial infection and propagation of HIV in lymph nodes, a blood donor becomes infectious (defined as day 0) with HIV RNA being detectable in plasma on days 14-15, HIV DNA detectable in leukocytes at day 17-20, and HIV antibodies detectable between days 20 and 25 (reproduced with permission from Busch [42]).
with HIV. They should be notified promptly because they often have high viral titers and may be at high risk for transmitting HIV infection. Counseling for persons with repeatedly reactive EIA and HIV antigen tests should incorporate arrangements for follow-up antibody testing.

Persons testing repeatedly reactive for HIV-1-Ag, but not confirmed by neutralization probably have a low prevalence of HIV infection. These people should be requested to return for repeat testing. If the donor is retested and found negative for the screening test for HIV-1-Ag, that donor could be considered for reentry. Donors can be reentered if they have been retested at least 8 weeks after their repeatedly reactive donation, and are found to be nonreactive for the HIV-1-Ag screening test and for the HIV antibody test. These donors could be counseled that their repeatedly reactive tests were reactive but that their supplemental tests were not confirmed, which likely represents a false-positive test. These donors can be reinstated as blood or plasma donors.

If a donor with a repeatedly reactive EIA and not confirmed HIV antigen test is retested after 8 weeks, and samples test repeatedly reactive on the EIA screening test and are not confirmed by neutralization, that donor could be temporarily deferred for 8 weeks as long as the HIV antibody test is negative. If a reinstanted donor tests repeatedly reactive on any subsequent evaluation subsequent to having been reinstated, that donor should be temporarily deferred again and is eligible for reentry 8 weeks or later. Such donors should be counseled that their repeatedly reactive tests were reactive on at least two donations (or samples) but that their supplemental tests were not confirmed. This may likely represent a false-positive test, but they are permanently deferred from being blood or plasma donors.

**HIV-1 Seroprevalence in Blood Donors**

When donor screening for anti-HIV was first introduced in 1985, from 0.1-0.8% of sera gave repeatedly reactive EIA results, depending on the location of the donor center and the reagents used; only 0.04% of donors were confirmed as positive by Western blot. During the second and third years of testing most centers reported repeat-reactive rates around 0.1-0.2% and confirmed positive rates of 0.01-0.04%. By 1992 the proportion of confirmed positives among donors had declined to 0.005-0.01% with an overall rate of 0.006%. More sensitive tests using PCR technology may detect additional potentially infectious donors. Following expected advances in automation and reliability, this technology may assume a role in future donor screening.

**Recipient and Donor Tracing (Look-Back)**

Identification of persons who have received seronegative or untested blood from a donor later found to be infected by HIV is referred to as “look-back.” Because the interval between infected transfusion and onset of AIDS can be very long, recipients are usually unaware of their infection and may be infectious to others. To identify these individuals, blood centers must have procedures to notify recipients of previous donations from any donor later found to have a confirmed positive test for anti-HIV, or a confirmed positive test for HIV-1-Ag. If a patient with AIDS is known to have donated previously, recipients of blood or blood products from these donations should be traced and notified. Recipient tracing and testing is usually done through the patient’s physician, not through direct contact with the patient. Look-back should start with the recipients of the most recent dona-
tions. If recipients of units (donated at least 6 months before the last known negative test) are tested and found negative, earlier recipients are probably not at risk, as infectivity earlier than 6 months before a negative screening test is extremely unlikely.

The FDA recommends the quarantine of previously collected units of Whole Blood, blood components, Source Leukocytes, or Source Plasma from any person who tests repeatedly reactive by screening test for HIV-1-Ag in the absence of repeatedly reactive screening tests for antibodies to HIV-1 and HIV-2.

**Human T-Cell Lymphotropic Viruses**

**Types of Viruses**

Human T-cell lymphotropic virus, type I (HTLV-I) was the first human retrovirus isolated and the first to be causally associated with a malignant disease of humans, adult T-cell lymphoma-leukemia (ATL). HTLV-I is also associated with the neurologic condition originally called tropical spastic paraparesis but now often called HTLV-associated myelopathy (HAM). Both these conditions occur in a small minority (no more than 2-4%) of persons harboring the virus, and they develop only after many years of infection. Infection during childhood is an important aspect of, possibly a requirement for, developing ATL, whereas childhood or adult infection can cause HAM.

Prevalence of HTLV-I infection shows striking geographic clustering, with pockets of high endemicity in parts of southern Japan, of sub-Saharan Africa, of the Caribbean basin, and of Brazil. Transmission is by sexual contact (predominantly male-to-female), by parenteral exposure to blood, and by mother-to-child transmission through breast milk.

**Clinical Observations**

For both HTLV-I and -II, infection persists lifelong, as does the presence of antibody. Studies of prevalence and transmission use seroconversion as the endpoint for diagnosis. Infection does not cause any recognizable acute events, and with the exception of those developing ATL or HAM, infected individuals experience no health consequences. Most carriers are asymptomatic and completely unaware of the infection.

**Transmission**

Both viruses are very strongly cell-associated. Contact with infected viable lymphocytes can cause infection, but plasma does not appear to be infective. Cellular components from infected donors cause seroconversion in 40-60% of recipients in Japan, but apparently in a much smaller proportion of US recipients. After refrigerated storage for 10 days or more, red cells from an infected donor are far less likely to cause seroconversion. Transfusion-transmitted HTLV-I infection has been associated with HAM of rather rapid onset.

**HTLV, Type II**

Human T-cell lymphotropic virus, type II (HTLV-II) was described several years after HTLV-I. There is at least 60% similarity of genetic sequences to HTLV-I, antibodies to either show strong cross-reactivity in tests with viral lysates. HTLV-II also shows clustering, but in different populations. High prevalence has been noted among some Native American populations and in intravenous drug users in the US, in whom seroprevalence is 1-20%. The only disease associated with HTLV-II has been HAM; occurrence seems to be somewhat less frequent than with HTLV-I.
Donor Tests

Donor screening for anti-HTLV-I began in the United States in 1989; at that time the rate of confirmed positive tests was 0.017%, a figure that has since declined as seropositive persons have been eliminated from the donor pool. The currently licensed EIA screening test does not accurately discriminate between anti-HTLV-I and anti-HTLV-II. Further testing of serum that is repeatedly reactive for anti-HTLV against antigen preparations specific for the two agents (HTLV-I or HTLV-II), or by PCR on material from peripheral blood mononuclear cells, can characterize the infecting agent. Half or more of blood donors reactive on EIA screening prove to have HTLV-II infections. A donation that is repeatedly reactive on EIA may not be used for transfusion. Although there is no requirement to perform additional testing, most centers do so, and if supplementary tests are positive (see Table 26-3), the donor is notified and permanently deferred.

Look-Back

Look-back is required for recipients of units drawn before the donor was found to be seropositive. Because recipients of units from seropositive donors do not consistently seroconvert, and because many seropositive donors have lifelong infection, the time frame for look-back is not self-evident. Five years or five previous donations was adopted as a reasonable approach, but if the earliest tested recipient proves to be seropositive, look-back should be continued backward. A definite separation between infective and noninfective donations is more likely to occur with donors who acquired infection as adults, usually through intravenous drug use or through sexual contact with intravenous drug users or with individuals from geographic areas of high prevalence. The screening requirement in place since 1989 has probably removed from the active donor pool most multi-unit donors with lifelong infection.

Cytomegalovirus

Cytomegalovirus (CMV) infection is widespread; transmission can occur through infectious body secretions, including urine, oropharyngeal secretions, breast milk, blood, semen, and cervical secretions. About 1% of newborns are infected, transplacentally or through exposure to infected cervical secretions at delivery or by breast milk. In early childhood, CMV is often acquired through close contact, especially day care settings; in adulthood, through sexual intercourse. Anti-CMV is present in 40-70% of healthy blood donors in the United States.

Clinical Observations

In persons with an intact immune system, CMV infection may be asymptomatic and remain latent in tissues and leukocytes for many years. Infection, either primary or reactivation of latent infection, can be associated with a mononucleosis-like syndrome of sore throat, enlarged lymph nodes, lymphocytosis, fever, viremia, viruria, and hepatitis. Intrauterine infection may cause jaundice, thrombocytopenia, cerebral calcifications, and motor disabilities; the syndrome of congenital infection causes mental retardation and deafness, and may be fatal.

CMV causes serious morbidity and mortality in premature infants and in recipients of organ and marrow transplants. Pneumonitis, hepatitis, retinitis, and multi-system organ failure are manifestations of infection, which can result from blood transfusions given to
Table 26-3. Recommended Actions for HTLV-I Testing

<table>
<thead>
<tr>
<th>First Donation to Be Tested for HTLV-I Antibodies</th>
<th>Subsequent Donation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EIA</strong></td>
<td><strong>Donation</strong></td>
</tr>
<tr>
<td>Repeatedly reactive</td>
<td>Destroy* all components</td>
</tr>
<tr>
<td>Repeatedly reactive</td>
<td>Destroy* all components</td>
</tr>
</tbody>
</table>

*Destroyed unless appropriately labeled as positive for HTLV-I antibodies, and labeled for laboratory research use or further manufacture into in-vitro diagnostic reagents.
†Assuming that separate prior donations have been repeatedly reactive for HTLV-I antibody no more than once. If separate prior donations had been repeatedly reactive for HTLV-I antibodies on two or more occasions, the donor should have been either permanently or indefinitely deferred.
many premature infants and to transplant recipients. Other causes, however, such as organ transplants from CMV-positive donors or reactivation of latent virus, may be as much or more of a risk than transfusion.

Transfusion-Transmitted CMV

Although over half of blood donors are CMV-seropositive, it has been estimated that less than 2% of these are able to transmit the virus. Posttransfusion hepatitis may, rarely, be due to CMV. The postperfusion mononucleosis syndrome that first focused attention on CMV in transfused components is now rarely seen. Posttransfusion CMV infection is generally of no clinical consequence in immunocompetent recipients.

Several categories of immunocompromised patients should be protected from risk of CMV transmission. These include low-birth-weight premature infants born to seronegative mothers; seronegative recipients of bone-marrow from CMV-negative donors; seronegative pregnant women, because the fetus is at risk of transplacental infection; and recipients of intrauterine transfusions. Often included in this category are seronegative recipients of any organ transplant from a seronegative donor; seronegative individuals who are candidates for autologous or allogeneic bone marrow transplants; and those few patients with AIDS who are free of CMV infection.

Preventive Measures

Blood from donors who test negative for CMV antibody has virtually no risk of transmitting CMV, but the supply of seronegative blood is limited. Another approach is to remove leukocytes from donated blood. Although the precise leukocyte population that harbors the virus has not been defined, leukocyte removal with high-efficiency filters (5 × 10^9 leukocytes per component, or less) can significantly reduce if not prevent posttransfusion CMV in high-risk neonates and transplant recipients. Other approaches are also important to consider, especially avoidance of unnecessary transfusions. Prophylactic therapy with CMV immune globulin and prophylactic use of antiviral agents are under scrutiny for high-risk immunosuppressed organ transplant recipients.

Other Viral Complications of Blood Transfusion

The transmissibility and clinical significance of other viruses and virus-like agents such as Epstein-Barr virus, human herpes virus 6, parvovirus, the agent of Creutzfeldt-Jakob disease, and others are being studied.

Epstein-Barr Virus

Epstein-Barr virus (EBV) causes most cases of infectious mononucleosis and is closely associated with the endemic form of Burkitt’s lymphoma in the Far East, and with nasopharyngeal carcinoma. Most persons have been infected by the time they reach adulthood; although usually asymptomatic, infection persists, remaining in B lymphocytes and oropharyngeal epithelium. Infection is spread by contact with infected saliva. Primary infection in children is either asymptomatic or is characterized by a sore throat and enlarged lymph nodes. Primary infection in older, immunologically mature persons usually causes a systemic syndrome, infectious mononucleosis, with fever; tonsillar infection, sometimes with necrotic ulcers; enlarged lymph nodes; hematologic and immunologic abnormalities; and some-
times hepatitis or other organ involvement. EBV infection targets B lymphocytes, which undergo polyclonal proliferation and then provide a T-lymphocyte response, seen as “atypical lymphocytes.”

Transfusion-transmitted EBV infection is usually asymptomatic, but has been a rare cause of the postperfusion syndrome that followed massive transfusion of freshly drawn blood during cardiac surgery and is a rare cause of post-transfusion hepatitis. EBV plays a role in the development of nasopharyngeal carcinoma and at least one form of Burkitt’s lymphoma, and has the in-vitro capacity to immortalize B lymphocytes. Although it contributes to the development of lymphoproliferative disorders in immunosuppressed recipients of marrow and organ transplants, there is no evidence that transfusion-transmitted EBV infection contributes to the development of malignancies in transfusion recipients.

Parovirus

Parovirus B19 is the cause of erythema infectiosum (fifth disease), a contagious febrile illness of early childhood. In adults, parovirus can infect and lyse red cell precursors in the marrow; sudden and severe anemia may occur in patients with underlying chronic hemolytic disorders. Infection during pregnancy imposes a risk, estimated to be less than 10%, of fetal infection, which causes severe anemia and consequent circulatory failure.

The red cell P antigen is the cellular receptor for parovirus B19, and people who do not have the P antigen are naturally resistant to infection. About 30-60% of normal blood donors have parovirus antibodies, which indicate immunity rather than chronic persistent infection. Viremia occurs only in the early phases of infection and there is no evidence for a carrier state. Transmission of parovirus through blood components other than clotting concentrates has not been reported.

Parovirus has been found regularly in clotting factor concentrates and has been transmitted to hemophiliacs. Because it lacks a lipid envelope, it is not reliably inactivated by solvent/detergent treatment, and it also resists heat inactivation utilizing temperatures below 100°C. The infection is usually without serious morbidity but hypoplastic anemia has been reported in HIV-infected hemophiliacs.

Colorado Tick Fever

Colorado tick fever is an acute viral illness acquired from tick bites in the mountainous regions of the western United States. The virus can persist in peripheral blood up to 90 days after symptoms disappear, but no chronic asymptomatic carrier state has been reported. The virus has been transmitted by blood transfusion. In the only reported case, the blood donor developed the febrile illness 4 days after removing an attached tick and 18 hours after donating blood. The virus was isolated from a segment of the donated blood after 2 weeks of storage and from peripheral blood of the recipient who had colon carcinoma and developed a prolonged febrile illness.

Tick-Borne Encephalitis Virus

Tick-borne encephalitis virus is a flavivirus transmitted by the bite of ticks from various parts of the world. One variety (Kumlinge disease) is restricted to southwestern Finland and nearby islands where 126 patients had serologic evidence of infection. Of these, three were laboratory acquired and two were acquired by transfusion. The blood donors became ill with Kumlinge disease.
only hours after donating but they neglected to inform the blood bank.

**Creutzfeldt-Jakob Disease**

Creutzfeldt-Jakob disease (CJD) is a fatal infection of the nervous system caused by a proteinaceous particle smaller than a virus. This infectious agent, now usually termed a prion, was once thought to be a slow virus because symptoms do not develop until many years after the initial infection. In the US, there is about one case of CJD per million people, nearly all in older individuals. In the vast majority of cases, the mode of acquisition is unknown. The agent causing CJD is resistant to commonly used disinfectants and sterilants. Fatal CJD has been transmitted through administration of growth hormone derived from human pituitary, transplantation of cornea, allografting of dura mater; and insertion of contaminated intracerebral electrodes.

Early experimental studies in animals and humans suggested the possibility that dementing illnesses such as Alzheimer’s disease and CJD could be transmitted by blood transfusion. This was based on the demonstration of the agent in human leukocytes and the development of degenerative changes at the intracerebral sites where human cells were introduced into hamsters or mice. Subsequent studies have failed to confirm transmissibility of Alzheimer’s disease through blood transfusion. This was based on the demonstration of the agent in human leukocytes and the development of degenerative changes at the intracerebral sites where human cells were introduced into hamsters or mice. Subsequent studies have failed to confirm transmissibility of Alzheimer’s disease through blood transfusion.

**Nonviral Infectious Complications of Blood Transfusion**

**Bacterial Contamination**

Bacterial contamination, one of the earliest recognized complications of stored blood, remains an important cause of transfusion morbidity and mortality. It accounted for about 16% of transfusion fatalities reported to the FDA between 1986 and 1991. No matter how carefully blood is drawn, processed, and stored, complete elimination of microbial agents is impossible. Bacteria are believed to originate with the donor, either from the venipuncture site or from inapparent bacteremia. Bacterial multiplication is more likely in components stored at room temperature than in refrigerated components, especially when room-temperature storage is in gas-permeable containers. Organisms that multiply in refrigerated blood and components are described as psychrophilic and are often gram-negative; gram-positive organisms are more often seen at room temperature. Strict adherence to phlebotomy protocols and scrupulous attention to sterile techniques during component preparation and storage should minimize contamination arising from sources outside the donor.

Infusion of bacterially contaminated components can cause a devastating septic reaction, with mortality rates up to 26%. In red cell components, the reactions may reflect the effects of endotoxin produced by such gram-negative organisms as *Pseudomonas* species, *Citrobac-*...
ter freundii, Escherichia coli, and Yersinia enterocolitica. Bartonella and Brucella species have also caused septic transfusion reactions.

Clinical Considerations

Severe reactions are characterized by high fever, shock, hemoglobinuria, DIC, and renal failure. If bacterial contamination is suspected, the transfusion should be stopped immediately and a Gram’s stain and blood culture should be obtained from the unit and recipient as promptly as possible after the reaction is observed. Color change to dark purple or black, clots in the bag, or hemolysis suggest contamination, but the appearance of the blood in the bag is often unremarkable. Bacterial multiplication may cause the oxygen in a red cell unit to be consumed, causing hemoglobin desaturation and darkening of the unit when compared with the color of cells in the attached sealed segments. The presence of bacteria in a Gram’s stain of the component is confirmatory, but absence of visible organisms does not exclude the possibility, especially if blood contained in attached segments was used for the Gram’s stain. The patient’s blood, the suspect component, and intravenous solutions in all the administration tubing used should be cultured for aerobic and anaerobic organisms at various temperatures.

Treatment should not await the results of these investigations, and should include immediate intravenous administration of antibiotics combined with therapy for shock, renal failure, or DIC if present.

Preventive Measures

Prevention of septic reactions depends upon reducing or preventing bacterial contamination of components. Careful selection of blood donors is the first and most important step.

The donor’s present appearance and recent history should be of good health; additional questioning may be needed if there is present or recent history of antibiotic use, of medical or surgical interventions, or of any constitutional symptoms. Questions to elicit the possibility of bacteremia are especially important for autologous donors, who may recently have had hospitalization, antibiotic therapy, or invasive diagnostic or therapeutic procedures; there have been several reports of Yersinia sepsis complications following infusion of stored autologous blood. At the time of donation, the temperature and pulse should be within normal limits.

There must be scrupulous attention to selection and cleansing of the donor phlebotomy site. Skin preparation reduces but does not prevent the contamination of components by bacteria. Scarred or dimpled areas associated with previous dermatitis or repeated phlebotomy can harbor bacteria and should be avoided.

Care in the preparation of components and handling of materials used in administration is essential. If a waterbath is used, components should be protected by overwrapping and outlet ports inspected for absence of trapped fluid, and the waterbath should be frequently emptied and disinfected.

The color and character of the component should be checked before release for transfusion. Some workers suggest comparing the color of blood in the container with that of the sealed segments. The extent of bacterial growth in platelet components correlates with the duration of storage. In recognition of improved platelet function resulting from improved containers and preservatives, in 1983 the FDA increased storage limits of platelets at room temperature from 3 to 7 days. In 1986, because of reports of
bacterial contamination in platelets stored longer than 5 days, the FDA reduced the room temperature storage limits for platelets to a maximum of 5 days.\textsuperscript{84}

Eventually, the use of detection systems may allow units to be monitored for contamination at the time of issue. Approaches under consideration include Gram’s stain, chemiluminescent probe systems, automated cultures, and demonstration of glucose consumption.\textsuperscript{85,86} Other strategies, such as prestorage leukocyte reduction, use of antibiotics in the storage media, and blood gas analysis of stored components, are also under investigation.

Malaria

Malaria is caused by several species of the intraerythrocytic protozoan genus \textit{Plasmodium}. Transmission usually results from the bite of an anopheles mosquito, but infection can follow transfusion of parasitemic blood. In the United States, malaria is probably the most commonly recognized parasitic complication of transfusion; the risk in the United States is estimated at 0.25 case per million transfusions.\textsuperscript{87} The species involved in transfusion-transmitted malaria in the United States are \textit{P. malariae} (40%), \textit{P. falciparum} (25%), \textit{P. vivax} (20%), and \textit{P. ovale} (15%).\textsuperscript{87} Fever, chills, headache, and hemolysis occur a week to several months after the infected transfusion; morbidity varies but can be severe, and deaths have occurred, especially from \textit{P. falciparum}.

Malaria parasites survive for at least a week in components stored at room temperature or at 4 C. The parasites can also survive cryopreservation with glycerol and subsequent thawing. Any component that contains red cells can transmit infection, via the asexual form of the intraerythrocytic parasite.

Asymptomatic carriers are the source of transfusion-transmitted malaria, although the parasite density is very low. Asymptomatic infections rarely persist more than 3 years, but asymptomatic \textit{P. falciparum} and \textit{P. vivax} infections may persist for 5 years, \textit{P. ovale} for 7 years, and \textit{P. malariae} can remain transmissible for the lifetime of the asymptomatic individual. There are no practical serologic tests to detect transmissible malaria in asymptomatic donors. Malaria transmission is prevented by deferral of prospective donors with increased risk of infectivity, based on medical and travel history. AABB Standards\textsuperscript{22} defers, from donation of red cells, persons who have had malaria in the preceding 3 years. Casual travelers to areas in which malaria is endemic are deferred for a year, but because early or prolonged exposure may reduce the incidence or severity of symptoms, immigrants, refugees, or citizens of areas in which the disease is endemic are deferred for 3 years after leaving the area.

Babesia

\textbf{Clinical Events}

Human babesiosis, caused by the intraerythrocytic parasite \textit{Babesia microti}, is the second most commonly reported transfusion-transmitted parasitic infection.\textsuperscript{88} Babesiosis is usually transmitted by the bite of an infected deer tick, from the coastal lands and islands of northeastern United States including Martha’s Vineyard, Cape Cod, and Long Island. Geographic areas of the hosts and the vectors appear to be expanding, along with expansion of the deer population.

The parasite can survive for up to 35 days at 4 C liquid storage, and has been transmitted by platelet components and cryopreserved red cells. In an area endemic for babesiosis, the risk of post-
transfusion babesiosis was found to be 0.17% for red cells; no cases were associated with platelets. Symptoms of transfusion-transmitted babesiosis are often so mild that the true nature of the infection may go undiagnosed; this may explain the small number of cases documented in the United States. In symptomatic cases, fever develops 1-4 weeks after infection, sometimes associated with chills, headaches, hemolysis, and hemoglobinuria. Rarely, the infection is life-threatening, due to rapidly progressive hemolytic anemia, renal failure, and disseminated intravascular coagulation. Asplenic or immunocompromised transfusion recipients are at greatest risk.

Preventive Measures

As with malaria, the Babesia carrier state may be asymptomatic. Persons with a history of babesiosis are indefinitely deferred, because lifelong parasitemia can follow recovery from symptomatic illness. More restrictive policies, such as not collecting blood in endemic areas in spring and summer months, when tick bites are more common, would probably have only limited value. No test is currently under consideration for mass screening to detect asymptomatic carriers of B. microti.

Syphilis

Syphilis is caused by the spirochete Treponema pallidum and is characteristically spread by sexual contact. The phase of spirochetemia is brief and the organisms survive only a few days at 4 C, so although transmission by transfusion is possible, it occurs very rarely. Syphilis transmission by transfusion is not prevented by subjecting the donor blood to standard serologic tests for syphilis (STS) because seroconversion occurs well after the phase of spirochetemia. Most positive STS results on donors reflect either immunologic abnormalities unrelated to syphilis (biologic false-positives) or inadequately treated syphilis that is more of a threat to the individual being tested than to a potential recipient. The STS is required as an indicator of potentially high-risk behavior that makes transmission of other organisms more likely.

Chagas’ Disease

American trypanosomiasis, or Chagas’ disease, is endemic in South and Central America and is caused by the protozoan parasite Trypanosoma cruzi. The human host sustains infection after the bite of reduviid bugs (called cone-nosed or “kissing” bugs), which usually exist in hollow trees, palm trees, and in thatched-roofed mud or wooden dwellings.

Clinical Events

T. cruzi infects humans whose skin or mucosa comes in contact with feces of infected reduviid bugs, usually as the result of a bite. Recent infections are usually either asymptomatic, or the very mild signs and symptoms go undetected. Rarely, the site of entry evolves into an erythematous nodule called a chagoma, which may be accompanied by lymphadenopathy. Fever and enlargement of the spleen and liver may follow. Recently infected young children may experience acute myocarditis or meningoencephalitis. Acute infection usually resolves without treatment, but persisting low-level parasitemia is usual and up to 20-40% of chronically infected people develop cardiac or gastrointestinal symptoms years or decades later.

Transfusion Considerations

In urban areas in which the disease is endemic, the second most common means of infection is transmission of T.
cruzi by blood transfusion. This may become a problem in the United States, as asymptomatic immigrants from these areas become blood donors. Three cases of transfusion-transmitted Chagas’ disease have been reported in the United States, in New York, Los Angeles, and Texas, all in immunocompromised recipients.

An EIA test for antibodies to T. cruzi as well as possibly confirmatory EIA and RIA tests are in development and should be submitted for licensure in the near future. Blood centers in areas with many immigrants from Central or South America have used questionnaires to identify potentially infectious donors; yields have been reassuringly low when donors whose replies indicated risk factors were screened by serologic testing. At present, it does not appear indicated to defer donors solely on the basis of questionnaires.

**Toxoplasmosis**

Toxoplasmosis is caused by the ubiquitous parasite *Toxoplasma gondii* and infection has been reported as an unusual transfusion complication in immunocompromised patients. The disease has not been considered a problem in routine transfusion practice.

**Lyme Disease**

Lyme disease is the most common tick-borne disease in the United States. *Borrelia burgdorferi*, the causative spirochete, is transmitted by bites of the deer tick. No transfusion-related cases have been reported, but chronic subclinical infections do occur and experimentally inoculated organisms can survive conditions of frozen, refrigerated, or room temperature storage. On the other hand, the phase of spirochetemia seems to be associated with symptoms that would render a potential donor ineligible, and in two reported cases where the donor became ill shortly after donation, the recipient did not develop infection. Potential donors who give a history of Lyme disease should be completely asymptomatic and should have completed a full course of antibiotic therapy before they may be permitted to donate.

**Parasitic Worms**

There have been occasional reports of parasitic worm infections transmitted by transfusion in countries other than the United States. Microfilarias is a potential transfusion risk in tropical zones, acquired by donors through bites by insects carrying *Wuchereria bancrofti* or *Leishmania* species.

**Reducing the Risk of Infectious Disease Transmission**

**Inactivation/Destruction of Agents in Components**

The first intervention specifically added to reduce the risk of hepatitis transmission was pasteurization (ie, heating to 60°C for 10 hours) used for albumin products since 1948. In those rare instances when infections have occurred with albumin or plasma protein fractions prepared with this step, the processing had been compromised. The plasma fractionation process used for immunoglobulin products employs cold ethanol precipitation, which concentrates HCV in the Factor VIII-rich cryoprecipitate and other fractions, and leaves little in the immunoglobulin fraction. The immunoglobulin fraction also has a high concentration of virus-neutralizing antibodies, and the resulting product has a remarkably low risk of virus transmission.
Immunoglobulins

Preparations of immunoglobulin intended for intravenous administration (IVIG) are expected to be similarly free of disease transmission. However, NANB hepatitis transmission did occur in the 1980’s during initial clinical trials of IVIG products in the United States and with routinely manufactured IVIG products in Europe. In late 1993 and early 1994, there were numerous reports of HCV infection in US recipients of an IVIG preparation from a single manufacturer, who did not use any virus inactivation procedures. During this period, HCV transmission did not occur from IVIG of other manufacturers or with intramuscular immunoglobulin.

Coagulation Factors

Until recently, clotting factor concentrates frequently transmitted viral infections. As the significance of HIV transmission became recognized, virus inactivation steps were applied more rigorously to concentrates of Factor VIII and other clotting factors. Unfortunately, a large proportion of the hemophiliac population receiving concentrates before processing was improved sustained HIV infection. Chronic hepatitis was an additional complication in almost all hemophiliacs receiving older clotting factor products.

The thermal instability of Factor VIII made it difficult to develop an effective heat treatment, until a practical approach was adopted in 1985. Since then, many disinfection steps have been introduced and factor concentrates are now, in general, very safe products. Each process has its own set of advantages and disadvantages. Application of organic solvents and detergents inactivates viruses with a lipid-containing envelope (eg, HIV, HBV, HCV, HTLV, EBV, CMV, HHV-6), but is ineffectiv
ing considered for transfusions of frozen plasma. The options under study include organic solvents and detergents, pasteurization, and use of photochemicals. Solvent/detergent treatment, effective against lipid-enveloped viruses, involves addition of 1% Triton X-100 and 1% tri-n-butyl phosphate (TNBP) to pooled plasma, followed by oil extraction of the TNBP and chromatographic adsorption of the Triton X-100. To protect Factor VIII during pasteurization, stabilizers are added and subsequently removed by ultrafiltration. Photochemicals such as methylene blue can be added to individual plasma units, which are then exposed to visible light. Of these three approaches, solvent/detergent treatment of plasma has been the best studied and validated.

**Processing Cellular Components**

The use of chemicals to inactivate viruses in red cell and platelet components is actively being studied but is not yet close to clinical application. Most inactivation protocols evaluated to date have employed photochemicals, photoreactive compounds added to the blood component, which is then exposed to light of a specific wavelength. These may act by generating reactive oxygen species that inactivate virus or by direct effects on nucleic acid.

**Reporting Transfusion-Associated Infections**

Unexplained infectious disease reported in a transfusion recipient must be investigated for the possibility of transfusion-transmitted illness. Hepatitis is expected to become apparent within 2 weeks to 6 months if it resulted from transfusion, but even within this interval the cause need not necessarily have been blood-borne infection. Blood centers and transfusion services must have a mechanism to encourage recognition and reporting of possible transfusion-associated infections. HIV infection thought to be a result of transfusion should also be reported to the supplier, although the interval between transfusion and the recognition of infection or symptoms may be years.

Infection in a recipient should be reported to the collecting agency so that donors shown or suspected to be infectious can be evaluated and recipients of other components from the implicated or other donations can be contacted and, if necessary, tested. A donor who proves to have positive results on tests during the investigation must be placed on a suitable deferral list.

The Code of Federal Regulations [21 CFR 606.170(b)] requires that fatalities attributed to transfusion complications (eg, hepatitis, AIDS, and hemolytic reactions) be reported to the Director, Center for Biologics Evaluation and Research (CBER), Office of Compliance, Division of Inspections and Surveillance, 1401 Rockville Pike, Suite 200N, HFM-650, Rockville, MD 20852-1448. A report should be made by telephone (301-594-1191) within one working day and a written report should be submitted within 7 days.

**Management of Posttransfusion Infections**

**Implicated Donors**

If documented transfusion-associated hepatitis, HIV, or HTLV-I occurs in a patient who received only a single unit, that donor must be permanently excluded from future donations, and the name be placed in a file of permanently deferred individuals. If posttransfusion viral infection occurs after exposure to blood from several donors, it is not necessary to exclude all of the potentially implicated donors. If only a few donors
are involved, it may be desirable to recall them to obtain an interim history and additional tests. If this is not feasible, a notation can be made in each donor's file that the individual was one of several donors (specify the number) involved in a case of transfusion-associated viral disease, and the names should be included in a special file of potentially implicated donors. Donors found to have been implicated in more than one case of transfusion-associated viral infection should be appropriately investigated and possibly deferred permanently according to procedures established by the collecting agency.

**Notification**

A donor who will be permanently excluded as a future blood donor, because of a positive test implication in post-transfusion viral infection, must be notified of this fact. Follow-up testing should, ideally, be done by the donor’s own physician, and the collecting agency should obtain the donor’s consent to release available information to a designated health-care provider. If the donor does not have a physician, a blood bank physician or other trained staff member should provide initial counseling and appropriate medical referral. The notification process and counseling must be done with tact and understanding, and the fears and concerns of the donor should be addressed. The donor should be told clearly why he or she is deferred and, when appropriate, about the possibility of being infectious to others. Notification should occur promptly because a delay in notification can delay initiation of treatment or institution of measures to prevent spread to others.

**Use of Immunoglobulins**

It is not recommended practice to give intramuscular or intravenous immune serum globulin or HBIG prophylactically to prevent posttransfusion hepatitis; these agents have not been shown to prevent posttransfusion hepatitis B, and the available evidence is conflicting about their effect on posttransfusion hepatitis C. If there has been inadvertent transfusion of known marker-positive blood, or needlestick exposure to infectious material, HBIG may prevent or attenuate infection.

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