Background: The transfusion of blood components plays a significant role as supportive therapy in the treatment of patients with cancer. Although blood transfusions help manage complications arising from either the patient's primary condition or associated with therapeutic intervention, their use introduces a new set of risks; therefore, health care professionals must be aware of the potential morbidity introduced by using blood components and endeavor to optimize outcomes by ordering transfusions only when the benefits outweigh the inherent risks.

Methods: This article sought to review the published literature, including the epidemiology of diseases transmissible via transfusion, performance characteristics for assays used for blood donor screening, surveillance activities to detect newly emergent pathogens, and biovigilance activities reported by public health authorities.

Results: Effective measures have been implemented to significantly decrease the risk of transmissible diseases associated with transfusion. Reports of viral disease transmitted via transfusion have been nearly eliminated, particularly since the introduction of molecular-based detection technology. The transmission of bacteria and parasites still represents a threat to the use of cellular blood components. Transfusion-associated human prion disease has not been reported in the United States. Immune-mediated reactions due to donor-recipient incompatibility remain a challenge.

Conclusions: Transmissible agents most commonly associated with risks due to transfusion are no longer a major threat; however, a significant challenge remains with regard to addressing the need for quick response mechanisms to manage emerging pathogens with the potential for rapid spread, either unintentionally (eg, globalization) or intentionally (eg, bioterrorism). The use of technology to reduce pathogens holds promise for further increasing the safety profile of blood transfusion.

Background

Although many of the risks associated with blood transfusions have been recognized ever since the beginning of the use of transfusions, the emergence of HIV transmission brought the safety of the blood supply into the limelight of the public. Since then, significant resources have been committed to implementing strategies to reduce the risk of transfusion-transmitted disease. Although challenges remain, significant advances have been made.

A tight, multilayered safety net has been woven into the system. Volunteer donors must meet strict criteria, aseptic techniques are used to collect blood in single-use disposable containers, testing is performed for various markers of present or past infection, and
passive and active biovigilance activities are in place before and after blood components are transfused.

In addition to the risk of transmissible diseases, blood components carry inherent risks associated with the presence of immunoactive effectors that interact with the host (blood recipient). These agents vary and can include immunoglobulins (antibodies), antigenic substances (phenotypes on cellular elements and plasma proteins), and various biological response modifiers (eg, cytokines, chemokines). Unlike chemical drugs and biological agents manufactured in a controlled pharmacological setting, blood components exhibit significant biological variability that impacts the achievement of desired outcomes as well as the manifestation of undesired adverse events.

When considering the safety of blood transfusion, one must discriminate between the safety of the product to be transfused (ie, the biological contents) and the safety of the transfusion process (ie, pre-transfusion testing, product administration, dosage, presence of indications or contraindications, risk vs benefit of such an intervention). In this manuscript, the aspects surrounding the safety of the transfusion product alone have been considered.

Transfusion-Transmitted Viral Agents

Hepatitis B Virus

Not long after the transfusion of whole blood or its components became available in routine medical and surgical treatments was its association with hepatitis virus infection recognized. The introduction of the test for hepatitis B surface antigen (HBsAg) in the early 1970s allowed the interdiction of units collected from individuals with either subclinical acute or chronic forms of the infection. However, the kinetics of the hepatitis B virus (HBV) infection leaves 2 different periods when screening for the presence of HBsAg fails to prevent transmission: (1) an early acute phase when the viral load is below the assay’s limit of detection, and (2) a late chronic phase when HBsAg levels gradually become undetectable although infectivity remains. The introduction of molecular techniques (nucleic acid testing [NAT]) decreases the serological period of infectivity by decreasing the limit of detection for the presence of the viral genome. Laboratories in numerous countries, including the United States, have also added a test to detect the presence of antibodies directed against a viral core protein (hepatitis B core antibody) to detect chronic carriers who may have levels of viremia below those detectable even by molecular techniques, a condition known as occult hepatitis B. The use of the 3 markers — HBsAg, hepatitis B core antibody, and HBV-NAT — has reduced the residual risk of transfusion-transmitted HBV infection to approximately 1 per 1 million donations, and the rate of clinical hepatitis continues to decrease as a larger segment of the population becomes immunized through vaccination.

Hepatitis C Virus

Following the implementation of first- and second-generation assays for HBsAg and the development of serological tests for hepatitis A virus, a distinct viral entity other than the 2 associated with the majority of cases of post-transfusion hepatitis was detected. After decades of work, hepatitis C virus (HCV) was molecularly characterized in the late 1980s using cloning techniques. It was a significant achievement because the virus could not be sustained in cell cultures. Screening tests were developed to detect the presence of anti-HCV antibodies and helped identify asymptomatic HCV carriers in the blood donor population. The use of the screening assay represented a significant advance because approximately 80% of individuals who become infected with HCV remain viremic for the remainder of their lives (unless treated). Most of these individuals are also asymptomatic for decades; by contrast, about 20% of those infected with HCV have spontaneous viral clearance. However, because of the prolonged seroconversion period, which lasts for more than 50 days, approximately 1 out of 230,000 donations with no demonstrable antibodies contain viral RNA. The introduction of NAT to detect viremia soon after a 10-day, ramp-up viral replication period has reduced the residual risk of transfusion-transmitted HCV infection to 1 in 1.93 million donations.

HIV

As the worldwide HIV epidemic unfolded, blood transfusion was recognized early on as an efficient means of HIV transmission. The emergence of this retrovirus focused attention on the safety of the blood supply and the importance of the development of rapid-response mechanisms to detect the rise of new threats to protect blood recipients. A serological test to detect the presence of anti-HIV antibodies was introduced in 1985 that allowed the interdiction of the vast majority of HIV-infected units. Similar to other screening assays based on the detection of donor seroconversion, infection in the donor could not be detected for approximately 22 days; however, this period was reduced by 11 days with the introduction of NAT. As a result, the residual risk of HIV transmission associated with transfusion has been reduced to 1 in 2.135 million.

West Nile Virus

West Nile virus is an emergent pathogen first isolated in samples obtained from patients in Uganda in 1937. Its presence was unknown on the North American continent until 1999 when it was found in patients diagnosed with neurological disease. Several species of mosquitos function as vectors for the virus, which...
finds its reservoir in migrating birds; humans and horses are accidental hosts. More than 90% of individuals infected with West Nile virus remain asymptomatic, and, of those affected, mild, flu-like symptoms without sequelae are the most common presentation; however, 0.6% of infected persons will progress to neuroinvasive disease that results in meningoencephalitis and possibly death. Individuals who remain asymptomatic but donate blood while viremic pose a risk to blood recipients, particularly among those who are immunosuppressed, the elderly, and infants. The risk of transmission is highest during the months when both the reservoir bird and mosquito populations peak, which occurs predominantly during summer, possibly extending to early fall in some regions of the United States. In 2002, the implementation of NAT for West Nile virus decreased the risk of transmission; however, residual risk rates are highly variable and depend on climactic and geographical factors that modify the location and duration of endemic areas. Annual reports indicate a paucity of cases linked to blood transfusion since 2010.

**Human T-Cell Lymphotrophic Virus**

The potential for HIV transmissibility through blood transfusion has raised concern about other retroviruses that, although they are not as pathogenic, could spread to the general population through the use of blood components. Two strains of human T-cell lymphotropic virus (HTLV), HTLV-1 and HTLV-2, were targeted for detection. Although HTLV-1 has been linked to adult T-cell leukemia, HTLV-associated myelopathy, and tropical spastic paraparesis, no firm link to disease entities has been found for HTLV-2. The virus is transmitted through cellular components alone and infectivity of the product declines with storage time, particularly when stored beyond 10 days. A total of 1% of those infected will develop disease associated with the infection. An immunoassay approved by the US Food and Drug Administration (FDA) is used to detect the presence of anti-HTLV-1 and 2 antibodies, although its rate of specificity is not optimal. The residual risk of transmission is low (1 in 3 million).

**Herpesvirus**

A significant segment of patients with cancer are particularly vulnerable to herpesviruses because of the immune compromise associated with cancer treatment. Cytomegalovirus (CMV) and human herpesvirus (HHV) 8 are cell-associated pathogens that can be transmitted through the transfusion of cellular blood components. Recommendations to mitigate the transmission include the use of CMV-seronegative, leukoreduced cellular blood components, or both. Although the clinical manifestations of transfusion-transmitted CMV have been reported, confirmed transmissions of HHV-8 via the same route have not been linked to the presentation of diseases known to be associated with it (eg, Kaposi sarcoma, malignant lymphoproliferative disorders).

**Parvovirus B19**

Infection with parvovirus B19, a nonenveloped erythrovirus, manifests differently in distinct patient populations. In utero, the infected fetus develops severe anemia that results in hydrops fetalis; in children, the infection results in the exanthematous fifth disease; and, in adults, it may result in mild disease, including fever, myalgia, rash, arthralgoby, and, occasionally, red cell aplasia in vulnerable individuals with ongoing hemolytic processes (eg, autoimmune or drug-related anemias, sickle cell disease). Concerns exist regarding the hypothetical possibility of the compromise of hematopoietic tissue engraftment due to parvovirus infection during the early transplantation stages; however, no reports of such associations have been published. The transmission of parvovirus B19 via transfusion has been documented, but morbidity has been limited, even in immunocompromised patients. This is despite epidemiological evidence that the virus is a relatively common contaminant in the blood supply and the incidence of transfusion-transmitted parvovirus B19 infection is likely under-reported.

**Hepatitis A and E Viruses**

Although hepatitis A and E viruses are both predominantly transmitted via the oral–fecal route, sporadic transmissions via blood transfusion have been reported. In most of the reported cases, mild, temporary liver inflammation has occurred. Because the incidence of transfusion-associated transmission is low in most developed countries (although some regions within developed countries may show significant endemicity rates), testing the blood supply is not warranted at this time. However, given that pathogen-reduction methods have not eliminated the risk of hepatitis A virus transmission, and the incidence of hepatitis E virus is increasing in Europe, implementing NAT screening methods is currently under investigation.

**Dengue and Chikungunya**

Both members of the *Arboviridae* family are expanding their traditional geographical boundaries together with the range of their vector, the *Aedes aegypti* mosquito, and both are poised to extend their range further as another member of the *Aedes* group (*A. albopictus*) is an even more efficient vector for the chikungunya virus when a specific mutation in the viral envelope is present.

Dengue virus is a mosquito-borne, single, positive-stranded RNA flavivirus with a wide distribution across the tropical and subtropical regions of the
world. Four serotypes of similar pathogenicity have been identified (a fifth serotype has been proposed but is pending further characterization). In specific regions, more than 1 serotype may coexist. Although the World Health Organization estimates that the disease burden is more than 100 million cases, this is likely an underestimation given the large population in the geographical span of its vectors. Typically, individuals infected for the first time develop fever, headache, muscle and joint pains, and a characteristics skin rash similar to measles. In a small proportion of cases the disease develops into life-threatening dengue hemorrhagic fever, resulting in thrombocytopenia, bleeding, and capillary leakage that may progress into dengue shock syndrome. The reason that some people experience more severe forms of dengue, such as dengue hemorrhagic fever, is multifactorial. Among the possible causes is a cross-serotypic immune response, which occurs when a person who was previously infected with dengue becomes infected for the second, third, or fourth time. Through a mechanism known as antibody-dependent enhancement, the previous antibodies to the old strain of dengue virus interfere with the immune response to the current strain, paradoxically leading to more viral entries and uptakes that correlate with the increased severity of the disease.

Chikungunya is an alphavirus with a positive sense, single-stranded RNA genome. Following a short incubation period, fever, intense headache, maculopapular rash, and severe joint and muscle pain ensue. An outbreak in the Reunion Island in the Indian Ocean, a region at the center of the historical range for the disease that extends from East Africa to Southeast Asia, was reported in 2005 to 2006. Given the development of tourism in the region, outbreaks traced to tourists returning from Reunion Island were later reported in Europe. Concerns about the extension of the endemic areas beyond the African and Asian continents have proven valid. Epidemiological surveillance has now identified cases in the Caribbean and sporadic outbreaks are occurring in the southeastern United States.

Reports of transfusion-transmitted dengue in endemic regions have been published, although no cases have been reported of chikungunya transmitted via blood transfusions. Due to the significant overlap between the regions where dengue and chikungunya and malarial parasites are endemic, travel abroad disqualifies most potential blood donors who return to the United States and are infected after being abroad. However, as the geographical range continues to extend for both viruses, the potential for blood-mediated transmission does exist. At the time of publication, no assays licensed by the FDA are available for either virus. Sporadic, local outbreaks of dengue have been reported in Hawaii, Florida, and South Texas, as well as chikungunya transmission in Florida. Through cooperation with public health authorities, surveillance and suspension of blood collection from areas affected have been successful in avoiding the spread of blood-borne infections in the United States.

Ebola

Ebola is a filovirus that has recently caused disease outbreaks in several West African countries. In addition, imported cases in the United States and Western Europe have been reported and are associated with health care workers returning from epidemic areas. Ebola is transmitted when an infected patient is symptomatic following the incubation period. Currently, individuals returning from Ebola epidemic areas are deferred from donating blood for 1 year because malarial travel restrictions apply to the same regions. To address the potential transmission through local contact, blood centers are also asking individuals who have been identified by public health officials as possibly exposed to a patient infected with Ebola virus not to donate blood for 28 days following the last contact with the infected person. No FDA-licensed assays exist to detect Ebola infection in donors. No cases of transfusion-acquired Ebola infection have been reported. The use of convalescent plasma for treatment remains investigational.

Bacterial Infections

Contamination of blood components with bacteria poses a significant challenge, particularly for platelets, because they cannot be stored at sufficiently low temperatures that have a bacteriostatic effect. The source of bacteria may be endogenous (eg, subclinical bacterial endocarditis, osteomyelitis, syphilis, dental abscess) or, more commonly, tied to a skin contaminant. In addition, during storage, the number of bacteria present in the container may continue to significantly increase up to the time of transfusion. The result may be that a sample from a unit of platelets cultured earlier (typically 24 hours following blood collection) does not necessarily reflect the current bacterial load prior to transfusion. Although alternative “close to release” assays have become available, none has proven to be practical for use outside of the nonemergent clinical setting. Currently, culture methods are capable of interdicting approximately 50% of contaminated units; however, most of the contaminated units not removed from inventory are transfused in the initial storage period before the bacterial load reaches concentrations that could have clinical consequences for the recipient. Therefore, while the rate of bacterial detection in platelet units is approximately 1 in 5,000, the incidence rate of significant morbidity associated with the transfusion of bacterially contaminated plate-
lets ranges from 1 in 70,000 to 118,000. The severity of the reaction depends on the amount of bacteria as well as their pathogenicity, which is associated with their capacity to induce septic shock and disseminated intravascular coagulation. In general, endotoxin-producing, gram-negative bacteria have a high correlation with significant morbidity and mortality.

The use of pathogen-reduction technologies applied to platelet components effectively eliminates the transfusion of units containing viable bacteria; however, no such technology has been licensed by the FDA for use in the United States.

Serological testing for syphilis has been performed since the early beginnings of transfusion. Treponema pallidum has been transmitted via transfusion when blood was reinfused within 24 hours of collection, and introducing serological testing for hepatitis rendered the practice of immediate use unfeasible, thus eliminating the transmission of syphilis through transfusion. Blood donors are still screened for syphilis, although no cases associated with blood component transfusion have been reported since the late 1960s.

Another member of the Spirochaeta family that has been the subject of studies is Borrelia burgdorferi, the causative agent of Lyme disease. Although the theoretical risk of transmission through transfusion has been posed, no case has been documented. Furthermore, in studies of recipients of components from DNA-positive donors, no evidence of infection was ever found.

Rickettsial agents may be transmitted via blood transfusion. These obligate, intracellular bacterial organisms remain viable even after 2 or more weeks of storage. The species and disease entities reported to be associated with blood transfusion as the exposure event are Anaplasma phagocytophilum (human granulocytic anaplasmosis), Coxiella burnetii (Q fever), and Rickettsia rickettsii (Rocky Mountain spotted fever). Given that the number of cases reported is low, no specific preventive measures beyond proper biovigilance are recommended.

Parasite Diseases With Possible Transmission via Blood Transfusion

Malaria

Because the number of autochthonous cases occurring in the United States in the last several decades has been limited to a handful, the risk of transmission is confined to the collection of blood from individuals who immigrate from or return from travel to endemic areas in which any of the 4 species of Plasmodium can be found. No assays have been licensed by the FDA to detect malarial parasites or antibodies in blood donors. Nevertheless, eliminating blood collection from at-risk individuals has reduced the risk of transfusion-transmitted malaria to approximately 1 in several million units. In the United States, about 5 cases of malaria associated with transfusion have been published since 2000. Most cases were traced to immigrants from endemic regions who then remained asymptomatic for several years after being considered successfully treated. Recipients of red blood cells from asymptomatic, infected donors develop symptoms 1 month or more following transfusion; because of the unusual transmission route and its protean clinical presentation, the diagnosis is typically made after ruling out several other potential causes.

American Trypanosomiasis (Chagas Disease)

The transmission of Trypanosoma cruzi via blood transfusion was recognized in endemic countries (mostly countries in the Western Hemisphere, except the United States and Canada) early after transfusion therapy became available. Seroprevalence studies conducted in Latin America have shown that 12% to 25% of seronegative recipients of fresh whole blood were found to seroconvert after receiving cellular blood components from infected donors. Detectable clinical disease 20 to 40 days after transfusion is more common in patients who are immunosuppressed; however, among immunocompetent recipients, approximately 30% of those who carry the parasite will develop cardiac or gastrointestinal clinical features characteristic of Chagas disease at least 20 years following transfusion.

Migrants from endemic areas were identified in 7 documented cases associated with transfusion in the United States and Canada, but more undetected, subclinical transmissions have likely occurred. As a result, blood establishments in both countries have implemented serological screening for all blood donors for the presence of anti–T cruzi antibodies to identify and interdict blood components with the potential for transmitting the parasite to recipients. Given this measure, the risk of transmission via transfusion is now considered negligible.

Babesiosis

The tick-borne intraerythrocytic parasite Babesia microti, as well as other closely related members of the Babesia species, such as B duncanii and B divergens, have been transmitted by blood transfusion in almost 100 reported cases, making this species the most frequently transmitted parasite via transfusion in the United States. The parasite uses wild rodents and deer as mammalian hosts and Ixodes ticks as vectors. In endemic areas of New England and the upper Midwest, serology surveys have found seroprevalence rates of around 2%, mostly for B microti. In western states, B duncanii is the predominant variant. The density of the deer population in suburban areas has increased in the last few decades, so the number of
donors carrying the parasite in their blood has also risen and resulted in more cases linked to transfusions every year. Patients who are immunocompromised or asplenic are vulnerable to a severe form of babesiosis, which is characterized by fever, hemolytic anemia, thrombocytopenia, and, in the most severe of cases, disseminated intravascular coagulation and multiorgan failure. Immunocompetent individuals who acquire the parasite either by tick bite or transfusion may remain asymptomatic or they may present with mild, flu-like illness. Asymptomatic individuals may remain parasitemic for months or even years. The FDA has not licensed any assays to detect current or past infestation in blood donors, so donor screening is limited to questioning potential donors about a prior diagnosis of babesiosis. Although the detection of parasites through NAT assays is the most effective way to interdict parasitic units, given its complexity and cost, the detection of antibodies to Babesia appears to be the most practical donor screening mechanism. At the time of publication, 2 different methodologies are under development.

**Leishmaniasis**

Leishmania donovani may be transmitted via transfusion and causes severe clinical disease in immunosuppressed and newborn recipients. At the time of publication, no assays reliably detect presymptomatic or asymptomatic infection. For that reason, intervention to prevent variant CJD transmission via transfusion is limited to the exclusion of donors exposed to regions where variant CJD has the potential to enter the food supply as the agent of bovine spongiform encephalitis, which infected cattle in the United Kingdom. This exclusion extends to individuals who spent at least 3 months in the United Kingdom from 1980 through 1996, at least 5 years in Europe since 1980, or those who received transfusions in the United Kingdom or France since 1980. The residual risk of infection with variant CJD in the United States is estimated to be negligible.

**Immune-Mediated Reactions**

**Hemolysis Due to Serological Incompatibility**

All transfusable blood components are labeled to indicate the blood type of the donor as well as the screening result for the detection of unexpected antibodies against red blood cell antibodies. Blood components containing plasma with unexpected (ie, other than anti-A and/or anti-B) isoagglutinins are not transfused. However, under certain circumstances, units of plasma or platelets incompatible with the red blood cells of the recipients may be transfused. To avoid hemolytic reactions under such circumstances (particularly for platelet components containing significant amounts of supernatant plasma), at least 1 of the following strategies should be used:

- Limit the total volume of ABO-incompatible plasma by restricting the total plasma volume to be transfused, reducing the plasma volume, or platelet washing
- Store in platelet additive solutions to reduce the residual plasma by two-thirds
- Obtain isoagglutinin titers to eliminate donors with high levels of hemolysins

**Transfusion-Related Acute Lung Injury**

Transfusion-related acute lung injury is most commonly associated with the transfusion of blood components containing a plasma volume that exceeds 100 mL. In more than one-half of observed transfusion-related acute lung injury, antihuman leukocyte antigen (anti-HLA) antibodies (classes 1, 2, or both) or antihuman neutrophil (anti-HNA) antibodies can be detected in the transfused product. Although the pathophysiology of transfusion-related acute lung injury has not been elucidated, the antibodies in the donor that interact with the leukocytes of the recipient are considered to be a significant risk factor. As a result, mitigation strategies involving the selection of donors not likely to have developed those antibodies (eg, untransfused men, women who have never
been pregnant or never received a transfusion) and testing donors more likely to have developed antibodies (eg, women who have been pregnant) have been developed. Although HLA antibody screening assays are available, no assays can be practically applied to detect anti-HNA. Furthermore, antibodies are not detected in a large number of cases of transfusion-related acute lung injury; thus, alternative pathways for neutrophil priming and activation involving lipid molecules, microaggregates expressing CD40 receptors, and microparticles formed during cellular component storage are underway.\(^46\)

**Graft-vs-Host Disease**

Graft-vs-host disease is a life-threatening complication of transfusion and is mediated by post-transfusion clonal amplification of the donor's lymphocytes in the recipient. This action occurs as a result of a patient's inability to suppress lymphocyte proliferation due to cellular immunodeficiency associated with his or her primary condition or immunosuppressive therapy. Vulnerable patient populations include premature infants, recipients of hematopoietic stem cell transplantation, patients treated with fludarabine, patients transfused with cellular components collected from direct blood relatives,\(^47\) and individuals with hereditary immunodeficiencies. Blood recipients included in any of the categories above should receive irradiated cellular blood components alone; the radiation dose must be sufficient to stop the clonal expansion of donor lymphocytes (estimated at 25 Gy). Pathogen-reduction procedures that use amotosalen followed by irradiation with ultraviolet light have been reported to be appropriate.\(^48\) The use of high-efficiency leukocyte depletion filters is not effective as a preventive measure.

**Additional Mitigation Strategies to Enhance Safety**

Although testing for markers of transmissible disease and applying special methods in the preparation of blood components provide a strong foundation and support the safety of the blood supply, blood establishments have implemented additional safety layers to enhance the therapeutic profile of transfusable blood components.

**Donor Recruitment and Selection**

The use of volunteer, nonremunerated blood donors is an effective means for obtaining safe source material for blood transfusion. To obtain donations from segments of the population with the lowest incidence levels for transmissible diseases, each donor must be subjected to an extensive medical questionnaire to assess his or her medical history, travel, and behavior associated with potential risks of exposure to pathogens that may be transmitted by transfusion. For example, travel to endemic areas for tropical disease temporarily disqualifies individuals until appropriate incubation periods have lapsed, and a history positive for viral hepatitis, drug use, or male-to-male sexual contact will result in indefinite deferral from blood donation under current US government regulations. Eligibility and disqualification criteria are established through governmental regulations as well as a set of standards established by professional societies. In addition, a physical examination that includes vital signs is also performed. All donors are provided with instructions to allow them to report potential prodromic symptoms of infection within 72 hours following donation.

**Leukocyte Reduction**

Current routine methods of filtration remove leukocytes from cellular blood components. Affinity filters that use physical properties as well as electrical static charges to remove the target cells are efficient devices that eliminate more than 99.999% of the white blood cells in the original blood collection with minimal loss of red blood cells or platelets.\(^49\) Using differential centrifugation, high-efficiency apheresis instruments are also capable of harvesting large numbers of platelets with minimal loss of white blood cells.

The depletion of leukocytes decreases the rates of immune sensitization and febrile nonhemolytic reactions. It also plays an important role in the prevention of CMV, HTLV-1, and HTLV-2 transmission and the removal of other intracellular pathogens.

**Pathogen Reduction and Inactivation**

The elimination of microorganism transmission through blood components is a goal of transfusion practice; however, the chemical or physical processes used to achieve that goal must maintain the viability and functionality of the treated product.\(^50\)

Plasma intended for transfusion may be treated with either methylene blue or solvent or detergent solutions. The former inactivates most viruses, bacteria, and parasites after forming stable chemical bonds when exposed to visible light. The latter acts by disrupting the membranes of most microorganisms with the exception of nonenveloped viruses such as hepatitis A and parvovirus B19. Both types of methods have been implemented in Europe for several years and one was approved for use in the United States in 2013\(^31\); however, neither method can be used on cellular components.

Platelet components may be treated with a psoralen (amotosalen) or riboflavin and then subsequently subjected to ultraviolet irradiation to stabilize the disruptive bonds made by those chemicals with DNA/RNA molecules. Pathogen-reduction systems for platelets are not available for use in the United States. An amotosalen-based system called Intercept (Cerus, Con-
cord, California) is in use in some countries in Europe and the Middle East, and Misrasol (Terumo BCT, Lake-wood, Colorado), which is a riboflavin-based system, is undergoing several clinical trials (NCT01740531, NCT01907906, and NCT00261924).

Given the high hemoglobin content in red blood cell components, methods requiring ultraviolet irradiation are not feasible. Although some chemicals have been identified that achieve significant pathogen-reduction levels, the potential formation of red blood cell neoantigens resulting in the immune destruction of treated cells has hampered progress. These systems are still in experimental phases.

**Biovigilance**

Procedures to quickly detect the possible spread of transmissible diseases via blood transfusion provide yet another safety layer for protecting the blood supply. Collaborating with public health officials by sharing surveillance data (eg, serosurveys of sentinel chickens for flavivirus outbreaks), investigating recipients of units from donors who seroconvert on subsequent donations (a process called “donor lookback”), or retesting donors who had their blood transfused to a patient who experienced a post-transfusion transmissible disease are some of the methods that can be used. In the laboratory, using samples from serial bleedings in recent seroconverted individuals provides valuable insights into the biology of infection with a particular pathogen and the different serological markers needed to detect infection in asymptomatic but infectious individuals.

**Conclusions**

Transmissible agents most commonly associated with risks due to transfusion are no longer a major threat; however, addressing the need for quick response mechanisms to manage emerging pathogens that may unintentionally or intentionally spread remains a challenge. The use of technology to reduce pathogens holds promise for further increasing the safety profile of blood transfusion.

In addition, blood transfusion plays an important role in supporting patients with cancer. A multilayered strategy has raised the safety profile of blood components to acceptable levels; however, treatment with blood transfusions must be considered within the broader context of risks and benefits that go beyond strict product safety. Many aspects related to the interactions between the allogeneic components transfused must be reviewed when assessing the risks and benefits of transfusion therapy for patients with cancer.

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