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Transmission of Diseases by Blood Transfusion

Siegfried Seidl, M.D., and Peter Kühnl, M.D.

Department of Immunohematology, University of Frankfurt, Frankfurt am Main, Federal Republic of Germany

A major risk of blood transfusion is transmission of infectious diseases. The pattern of these diseases varies in different parts of the world. This article reviews the viral, bacterial, and parasitic infections that can be transmitted by transfusion of blood or blood products. A major part of the article deals with posttransfusion hepatitis, the most frequent complication.

A large number of screening techniques have been introduced by blood banks to detect transmissible diseases. Apart from these procedures, the most effective "screening test" is adequate selection of prospective donors, ensuring that they are in good health and that their history does not indicate risk of transmitting a disease [1].

Viral Diseases

Posttransfusion Hepatitis

The disease was originally described as "serum hepatitis" but was later modified to "posttransfusion hepatitis" (PTH). There are at least 2 hepatitis viruses known to be transmitted through blood and blood products: hepatitis B virus and the agent(s) of non-A, non-B hepatitis. Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) infections are discussed later in this article as causes of PTH.

Incidence. In most prospective studies, the patients involved have undergone cardiac surgery. These patients receive many units of blood and this may result in an overemphasis of the risk of PTH. The data show that only a few cases of PTH are still caused by hepatitis B; 78–100% of the observed hepatitis patients suffered from hepatitis non-A, non-B (hepatitis NANB). A high prevalence (8–17%) of PTH has been reported from Sweden, Spain, Italy, the United States, and Israel, whereas low percentages (2–5%) were observed in Australia, Finland, and West Germany. Other prospective studies included hospitalized patients in whom cardiac surgery was *not* performed. In the United States, the Transfusion Transmitted Virus (TTV) Study Group [2] summarized the data of the 4 participating centers, covering a wide geographical range. The hepatitis attack rate was 11.3%, with a range from 4.0% to 18%. More than 90% of the PTH cases were due to infection with the NANB agent(s). A similar incidence of hepatitis NANB has been observed in the Dutch study [3] although the overall hepatitis frequency was only 3.9%. The figures reported from Japan [4] are in agreement with the American data; hepatitis incidence was 11.5%. Of these, there were 92.8% due to infection with the NANB agent(s).

Hepatitis B. The discovery of the hepatitis B antigen (HBAg) provided an excellent immunological tool for the study of PTH. Electron-microscopically, 3 types of particles may be visualized in the serum of an HBsAg-positive person. The most numerous are small 20-nm spheres, followed by tubules 20 nm in diameter and up to 100 nm long (representing the surface antigen) and DANE particles which are considered to be the complete virus. The inner core has a distinct antigenic determinant, the hepatitis core antigen (HBcAg). The corresponding and specific antibodies are anti-HBs and anti-HBc, respectively. A third antigen–antibody system, consists of HBeAg (probably also located in the core of the DANE particle) and anti-HBe.

A further antigen, the delta antigen [5], is hepatitis B virus-associated. It is rarely found in blood donors, but common in addicts who take drugs parenterally. The prevalence of HBsAg carriers varies considerably in different parts of the world. A low incidence, approximately 0.1% of HBsAg, occurs in western Europe, Scandinavia, and North America, while carrier rates of up to and in excess of 10% have been reported for Africa and Southeast Asia.

Figure 1 shows the typical course of hepatitis B infection. Icterus develops 50–180 days after infection, preceded by transaminase elevation and the occurrence of HBeAg and HBsAg. Both antigens disappear approximately 4–6 weeks later, followed by the appearance of anti-HBe, whereas anti-HBs is detectable after another 4–8-week interval. Anti-HBc is usually found in serum long before anti-HBs and both may persist for years, thus indicating a previous hepatitis B infection. In chronic infection HBsAg remains detectable for many years, perhaps for the entire life of the individual. Anti-HBc is also present.

Hepatitis (NANB). The failure of a specific assay for the detection of hepatitis NANB probably reflects 2 factors: (a) the

Reprint requests: Prof. Dr. S. Seidl, Department of Immunohematology, University of Frankfurt and Red Cross Donor Service Hessen, Sandhofstr. 1, B.P. 730369, D-6000 Frankfurt/M., Federal Republic of Germany.

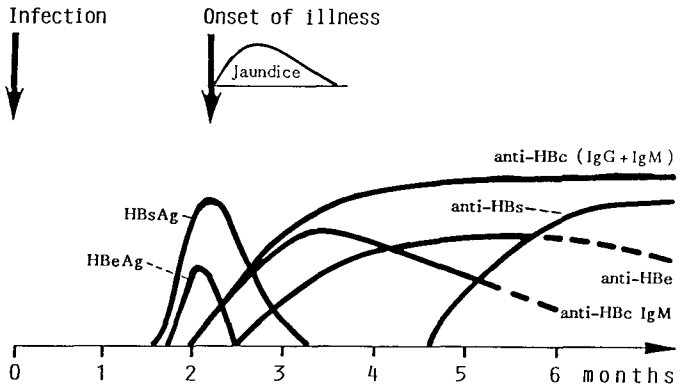

Fig. 1. Hepatitis B infection. Occurrence of hepatitis B markers in various periods of the disease. Modified from [28].

low level of viremia (which implies a low level of specific NANB antigen), and (b) due to the chronicity of this disease, high titer antibody is extremely rare [6]. Since specific screening procedures are not available, it has been suggested that indirect tests (surrogate tests) might serve as interim screening measures. Alanine aminotransferase (ALT) testing and screening for anti-HBc has been suggested. It was assumed that these 2 markers would identify the same NANB carrier population. This, however, has not been confirmed recently [7].

Control. A number of methods are available to control PTH.

1. Blood Donor Screening. Today there is general agreement that only tests of "third generation" sensitivity should be employed: reverse passive hemagglutination (RPHA) technique, enzyme immunoassay (EIA), and radioimmunoassay (RIA). Both EIA and RIA are widely used in blood transfusion services and detect up to 1.0 ng/ml HBsAg [8].
2. Inactivation of Hepatitis Viruses in Blood Products. After cold ethanol fractionation, the isolated plasma protein fraction (PPF) or albumin is heated (10 hours at 60°C), which accounts for the "hepatitis safety," i.e., these products do not transmit hepatitis. This process is not applicable to immune globulin preparations, but this plasma derivative is considered to be hepatitis safe due to the presence of antibodies against the various types of hepatitis viruses. Heating (10 hours at 60°C) has also been applied to sucrose-glycine solutions of factor VIII [9]. Chemicals have also been used. With a combined β-propiolactone-ultraviolet (beta-PL/UV) irradiation procedure [10], a factor IX concentrate is prepared, which did not cause hepatitis in susceptible chimpanzees and human volunteers. Recently, another approach has been reported consisting of exposure to Tween 80 and ether [11].
3. Passive and Active Immunization. Two preparations are available: immune serum globulin (ISG), prepared by cold ethanol fractionation of large pools of plasma from normal blood donors, and hepatitis B immune globulin (HBIG), derived from selected donors with high anti-HBs titers. Administration of ISG can prevent hepatitis A. This type of hepatitis, however, is not transmitted through blood and blood products. The best established indication for HBIG administration is postexposure prophylaxis after a single acute exposure to hepatitis B virus as may occur in accidental inoculation (needle-stick), after oral ingestion, or a splash with HBsAg positive blood on mucous membranes. Prophylaxis should be performed as soon as possible (within 2 days after exposure) and 4 weeks later.

Without specific tests for antibodies against hepatitis NANB it is difficult to estimate the potency of an immune globulin preparation for the prevention of hepatitis NANB. In a recent study [12] performed in patients undergoing open-heart surgery, a final conclusion on the HBIG efficacy could not be reached, although there was a trend toward a lower frequency of PTH NANB in patients receiving HBIG.

With regard to active immunization, hepatitis B vaccine is available, developed by American and also by French workers. These vaccines consist of highly purified HBsAg particles obtained from HBsAg carriers. The material is treated with formalin to inactivate any live virus. Both vaccines have been extensively evaluated for safety, immunogenicity, and efficacy. After 3 injections of the American vaccine, the anti-HBs response rate was 96%. Similar data have been obtained with the French vaccine. Neither viral hepatitis nor the acquired immunodeficiency syndrome (AIDS) have been transmitted through hepatitis B vaccines.

Cytomegalovirus (CMV)

Human cytomegalovirus (CMV) is a member of the herpes virus group, which also includes Epstein-Barr virus (EBV), varizella zoster virus (VZV), and herpes simplex virus type I and type II (HSV I, HSV II) [13]. CMV is transmitted vertically and horizontally by sexual contact, blood transfusions, organ transplants, or from mother to child and can persist life-long as a latent, sometimes reactivated infection. The agent is capable of producing a heterophil antibody-negative syndrome which closely resembles infectious mononucleosis (IM) after blood transfusions, in particular, 1 or 2 months after open-heart surgery ("posttransfusion mononucleosis" or "postperfusion syndrome").

CMV disease can occur as primary infection, which can be symptomatic in seronegative recipients of a latently or actively infected donor's blood; as reactivated infection, largely asymptomatic in seropositive recipients of a seropositive or seronegative blood unit; as reinfection with a CMV strain different from the one originally infecting the recipient.

Laboratory diagnosis of CMV infection can be established by a variety of methods: (a) screening for CMV antibodies in serum by liquid or solid-phase assays, i.e., complement fixation (CF), indirect fluorescence assay (IFA), indirect hemagglutination (IHA), enzyme-linked immunosorbent assay (ELISA), and radioimmunoassay (RIA); (b) microscopy (nuclear inclusion bodies in giant cells), electron microscopy, cytopathic effects in cell cultures, DNA and polypeptide analysis for CMV strain identification; and (c) T helper/suppressor cell ratio, lymphocyte stimulation by CMV antigens, antibody kinetics of B cells, and measurement of interferon.

Severe posttransfusion infections occur preferentially in certain groups of immunocompromised hosts, i.e., premature infants with a birth weight of $< 1{,}300$ g, who frequently receive multiple transfusions from seropositive donors; seronegative infants lack maternal antibodies and acquire CMV infections in 30% of all cases with a high mortality of 25%; kidney or bone marrow transplant recipients, who acquire CMV via the graft or

blood products; patients after splenectomy; immunocompromised oncology patients; and infants with congenital immune deficiencies.

On the basis of neonatal studies and clinical data, seronegative blood products (or grafts) are indicated in seronegative high-risk patients. Passive immunization may be the only long-term answer to prevent severe or fatal CMV infections.

Epstein-Barr Virus (EBV)

Epstein-Barr virus (EBV) is another member of the herpes virus group and prevalent among the general population. By oral infection, infected saliva, and respiratory transmission, the agent causes infectious mononucleosis (IM). Like other herpes viruses, it remains latent in white cells; a viral carrier state ensues. It is closely associated with Burkitt's lymphoma and nasopharyngeal carcinoma.

EBV can be transmitted by infected blood, although transfusion-transmitted infections do not add significantly to the high prevalence of this agent. The seropositivity rate increases rapidly during infancy and reaches values of 90% in adults, depending on socioeconomic conditions [14]. In immunocompetent EBV-negative recipients, an EBV exposition through blood is symptomless due to a simultaneous passive transfer of protective EBV antibodies and an efficient elimination of EBV-infected donor B cells by the recipients' T-cells. Symptomatic EBV transmission may occur only under rather limited conditions: (a) transfusion of a single unit of blood from a donor during incubation of IM (additional units would contain protective EBV-antibodies with a high probability); (b) presence of (nonprotective) antibodies against the EB viral capsid antigen (VCA) only, at absent or inadequate levels of protective EBV-neutralizing antibodies [15]; and (c) a T-cell deficiency of the recipient. Immunosuppressive therapy after organ transplantation represents an important cofactor for the manifestation of IM-like illnesses. Leukocyte transfusions carry the greatest risk of EBV contamination [16].

Other Herpes Viruses

In contrast to CMV and EBV, which have their persistent habitats in blood-borne cells (leukocytes, B-lymphocytes), the 3 other members of the group of herpes viruses, herpes simplex type I and II (HSV-I, HSV-II), and the varizella zoster virus (VZV) are predominantly neurotropic. Primary infections with viremia usually occur in childhood, and reactivations of latent infections in adults are often febrile. This contributes to the fact that these viruses have not been linked with a particular disease transmissible through blood.

Human T-Lymphotropic Virus Type I

HTLV-I (human T-lymphotropic virus type I) represents the first human retrovirus, and may be the first direct human tumor virus closely linked to a particular form of T-cell malignancy, the adult T-cell leukemia (ATL). HTLV-I antibodies were detected in almost all ATL cases in the United States and in Japan. ATL affects both sexes with a male excess (1.5/1.0) of adults aged mainly from 40 to 65 years, with or without leukemic changes (acute, chronical, smouldering). The homogeneity of the clinical patterns suggests a specific tropism of HTLV-I for a particular subset of T-cells (OKT 4+) which experiences malignant transformation. The positivity rates are influenced by social class and the relationship to lifetime sexual partners.

Important modes of infection are apparently by sexual transmission, perinatally from mother to child, and by blood transfusions. Reports on transfusion-induced HTLV-I antibody seroconversion came from Okochi and Sato [17]. In this study from Japan, 585 seronegative recipients were eligible for analysis of the relationship between blood units transfused and seroconversion: 480 (group 1) received HTLV-I antibody-negative blood units, 20 (group 2) HTLV-I antibody-positive fresh frozen plasma. Patients of both groups remained seronegative. In contrast, 53/83 (63.9%) recipients of at least 1 unit of anti-HTLV-I-positive blood (whole blood, packed red cells, or platelets concentrates) in group 3 developed HTLV-I antibodies 3–6 weeks after transfusion. In view of the total number of patients enrolled in the study, 9.1% (53/585) became positive. The storage period was found to have a significant influence. Twenty of 24 units of packed red cells stored $\geq$ 4 days resulted in the production of anti-HTLV-I antibodies in 20 recipients, while only 21/44 units of packed red cells stored $>$ 5 days did so in 21 recipients. No cases of ATL due to HTLV-I infection acquired by blood transfusions have been reported so far, possibly due to a long latent period between infection and development of ATL.

Compared to the public health benefits of LAV/HTLV-III antibody screening in blood donors, similar positive effects cannot be forecast by HTLV-I antibody screening, even in endemic areas where HTLV-I contributes substantially to the leukemia/lymphoma risk of the population.

Human T-Lymphotropic Virus Type II

A second human retrovirus also belonging to the subfamily of oncovirinae, termed human T-cell leukemia virus type II (HTLV-II), was isolated from a patient with a T-cell variant of hairy cell leukemia [18]. A linkage of HTLV-II to a major disease causation has not been established so far.

Neurotropic Slow Viruses

Concern has been maintained about the possibility of transmitting so-called neurotropic slow viruses by transfusions, inducing chronic degeneration CNS diseases like Creutzfeld-Jakob disease (CJD), Kuru, or a rare sequela of measles virus infection, subacute sclerosing panencephalitis, after many years of latency [16]. Whereas Kuru has been observed only in the highlands of New Guinea, 1,453 cases of CJD had been observed as of 1979 in different parts of the world. The risk of neurotropic slow-virus infections (except of LAV/HTLV-III) is difficult to assess with specific serological tests yet to be developed [19].

Serum Parvovirus-Like Virus

Normal children remain symptom free or may show only short fever and erythema after the apparently very common infection with human paravovirus (serum parvovirus-like particles =

SPLV; synonymous: Aurillac antigen or B19) [20, 21]. More than a third of the normal population have anti-SPLV antibody before the age of 16. SPLV was found to be the cause of aplastic crisis in patients with chronic hemolytic anemias, e.g., sickle-cell anemia, hereditary spherocytosis, thalassemia, and pyruvate kinase deficiency. A special affinity of SPLV for red cell precursors seems to be the underlying mechanism in chronic hemolytic anemias, whereas healthy SPLV-positive donors are hematologically symptomless. In hemophiliacs, the treatment with factor VIII concentrate induces specific SPLV antibodies in 97%. The short period of SPLV viremia, mostly in infancy, suggests a minimal risk of virus transmission by blood transfusions, similar to that of hepatitis A.

Exotic Tropical Viruses

Individuals with a recent history of travel in Africa, South and Central America, or Southeast Asia may transmit tropical viruses by blood transfusions and are, therefore, temporarily excluded from blood donations. Travelers returning from areas endemic for malaria are excluded for 6 months, according to AABB regulations, a fact that also helps to prevent the transmission of some arthropod-borne virus infections that may be acquired on most continents [16]. Regardless of the travel history, recent febrile illnesses cause a deferral of the prospective donor.

Parasitic Infections

Malaria

Transfusion-associated malaria is frequently observed in endemic malarial countries but may also constitute an increasing risk to western countries due to "import" of the disease by returning travelers. Transmission occurs not only after whole blood, but also after transfusion of blood components. Although *Plasmodia* may survive in frozen blood for years, the risk of transmitting malaria decreases with increasing storage time. In previous years most of the reported cases of posttransfusion malaria were associated with *P. malariae* infection, but a recent survey indicates that *P. vivax* has become more common and that *P. falciparum* frequency has quadrupled to 20% [22]. The morbidity and mortality caused by different species vary considerably; however, life-threatening infections occur mainly with *P. falciparum*. Screening techniques have therefore been designed primarily to eliminate *P. falciparum* carriers.

A promising strategy for the direct detection of blood parasites has been initiated by French workers [23], using monoclonal antibodies for indirect immunofluorescence and for an enzyme-linked immunoassay (EIA). Another approach to malaria diagnosis has been proposed by a Swedish team [24], using the capacity of a DNA probe containing cloned repetitive sequences from *P. falciparum*. An enzyme immunoassay has also been used for detecting antibodies against *P. falciparum* [25].

Filariasis

Microfilariae can survive in refrigerated citrated blood for at least 14 days, and have been demonstrated in the blood of recipients for years after transfusion. Since the development of adult worms requires passage through an insect vector, the typical clinical symptoms of filariasis are not observed after transfusions of infected blood. Fever, headache, and rash were reported as a host response to transmittal of the organisms. At least 5 species of filariae may be transmitted by blood transfusions: *Wucheria bancrofti* and *Acanthocheilonema perstans* (endemic in tropical Africa and Latin America), *Mansonella ozzardi* (Latin America), *Loa loa* (Africa), and *Brugia malayi* (Southeast Asia). An estimate 180–400 million people in the world are infected with *W. bancrofti*.

Trypanosomiasis and Leishmaniasis

Chagas' disease ("American trypanosomiasis") is a parasitic disease caused by *Trypanosoma cruzi*, a small fusiform protozoan transmitted by the feces-contaminated bites of triatomial insects (reduviid bugs). Fifty percent of seropositive individuals also have parasitemia and present a risk of transmission by blood and plasma transfusions, the second most important mechanism of *T. cruzi* transmission [26].

Chagas' disease occurs only in the Americas, from Mexico to the central part of Argentina, and also in the southern United States. It is estimated that more than 12 million people in Central and South American are infected [27] and the prevalence of the disease is as high as 9% in some Latin America countries.

Blood transfusion represents an important means of transmission because refrigerated blood can remain infective for 3 weeks, although stored blood (> 10 days) is considered safer than fresh blood. Several data show that between 12 and 50% of blood recipients may become infected. The disease has been called one of the most important transfusion hazards in South America. Serologic testing is mandatory for blood banks in many Latin American countries. Several tests are available for donor screening; the indirect hemagglutination (IHA) and the indirect immunofluorescence tests (IIF) are the most widely used.

Visceral leishmaniasis (or kala-azar) and African trypanosomiasis may be transmitted by blood transfusion, but this mode of transmission appears to be uncommon even in endemic areas. The majority of reported transfusion cases are in children.

Toxoplasmosis

Toxoplasmosis is a parasite infection caused by *Toxoplasma gondii* with a worldwide distribution (up to 80% of potential blood donors in the United States) [16]. Transplacental transmission without detectable disease is the most frequent type of infection. In rare cases, the disease (with CNS and visceral involvement) has also been transmitted through blood and blood products, particularly through leukocyte concentrates in severely immunosuppressed patients with hematologic malignancies or AIDS. Patients with thalassemia major who are recipients of multiple transfusions have been shown to have 6 times the prevalence of antitoxoplasma antibodies compared to an age-matched normal population. Although serologic methods are available, these techniques are not widely employed.

Babesiosis

The organism *Babesia microti* can be transmitted by blood transfusions and may be responsible for unsuspected cases of babesiosis. *B. microti* is a parasite of red blood cells and can survive in blood stored at 4°C or −20°C. It can be transmitted by blood from donors who reside in or have visited certain areas in the northeastern United States and have become infected by deer ticks.

The incubation period is approximately 4 weeks, the maximum period of parasitemia 4–6 months. The majority of *B. microti* infections is asymptomatic, whereas splenectomized or immunosuppressed recipients may develop a severe and sometimes fatal hemolytic anemia and renal failure. Serologic tests based on indirect immunofluorescence reveal positive antibody titers in up to 3% in endemic areas and active infection in 0.3%.

Bacterial Infections

Syphilis

In the early days of transfusion therapy when blood was directly transfused from the donor to the recipient, syphilis was recognized as a serious hazard. With the use of stored and refrigerated blood, this complication has virtually disappeared.

Several serological tests are in use to detect syphilis infection in blood donors. Fluorescent *Treponema* Antibody Absorption (FTA-ABS) and *Treponema pallidum* Hemagglutination (TPHA) are slightly better than the cardiolipin test.

Gram-Negative and -Positive Organisms

For prevention of bacterial contaminations in blood, the use of closed collection systems and disposable equipment has proven an effective means. Special measures are advisable if open collection is still in use, e.g., sterilization of blood bank equipment, careful skin disinfection, and scrupulous attention to the handling of needles and tubing. Continuous storage of blood at 4°C, exclusion of donors with identifiable infectious diseases by history and physical examination, and temporary donor deferral (24 hr) after dental extraction represent further means for reducing the risk of bacterial infections transmitted by blood [16]. The bactericidal capacity of stored blood prevents the contamination of a blood unit by specific and unspecific antibodies, complement, and phagocytosis during the first 12 hours of storage. The ability of fresh blood to "sterilize itself" clearly depends on the size of the bacterial inoculum. On the other hand, the immunologic status of the recipient determines whether a small number of pathogenic microorganisms can be inactivated and eliminated or may lead to a fatal sepsis. Accidental minor bacterial contaminations may lead to massive contamination if the organism grows at temperatures at which the blood is stored (2–6°C; so-called psychrophilic organisms like some *Pseudomonas* species), and if they can utilize the salts of citric acid as a carbon source (gram-negative organisms like *Escherichia freundii*).

Specific Organisms

Among the group of specific organisms, brucellosis, rickettsial disease, and leprosy deserve special attention. Infections with *Brucella abortus* by transfusing contaminated blood from asymptomatic, apparently healthy blood donors were reported. Immunocompromised recipients and splenectomized thalassemic patients are at risk to develop a mononucleosis-like illness. The exclusion of donors with *Brucella* agglutinin titers of > 1:1,000 or a history of brucellosis in the past 2 years has been recommended. No transfusion-transmitted brucellosis has been reported in the United States [16].

The transmission of rickettsial diseases is possible during the active stage, whereas the organisms are absent in blood during remission. A case of Rocky Mountain spotted fever (*Rickettsia rickettsii*) in a recipient of blood collected during the incubation period has been reported.

Leprosy (*Mycobacterium leprae*) is considered a potential transfusion problem in Africa, Asia, and Latin America, although little is known about the effects of transfusing lepromatous blood.

For diagnosis of bacterial infections transmitted by blood, visual and olfactory examination (hemolysis, odor of hydrogen sulfide) or a blood sample from the transfusion unit, a Gram stain and wet smear for light microscopy, and blood cultures from the patient and blood bag or pilot tube at 4°C, 20°C, and 37°C should be performed to distinguish bacterial complications from transfusion reactions due to blood group incompatibilities between donor and recipient.

Résumé

Un risque majeur de la transfusion sanguine est la transmission éventuelle de maladies infectieuses, L'échantillon de ces maladies varie dans les différentes parties du monde, L'article passe en revue les infections virales, bactériennes et parasitaires qui peuvent être transmises par la transfusion de sang total ou de parties constituantes de sang. Une large part de l'étude est consacrée à l'hépatite post-transfusionnelle qui est une des complications les plus fréquentes.

Resumen

Riesgo principal de la transfusión sanguínea es la transmisión de enfermedades infecciosas. El patrón de tales enfermedades es variable en las diferentes partes del mundo. En este artículo se hace una revisión de las infecciones virales, bacterianas, y parasitarias que pueden ser transmitidas por transfusión de sangre o de productos sanguíneos. La mayor parte del artículo hace referencia a la hepatitis postransfusional, la más frecuente entre las complicaciones.

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