Review

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Hazardous Clinical Conditions Present Specific Transfusion-Transmitted Disorder Risks and Require Special Attention: Sickle Cell Disease, Transplantation Settings

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Hazardous Clinical Conditions Present Specific Transfusion-Transmitted Disorder Risks and Require Special Attention: Sickle Cell Disease, Transplantation Settings

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Abstract

Aims: The aim is to focus on the risk of transfusion-transmitted diseases, which are appearing in really endangered conditions, especially in hazardous disorders like sickle cell disease, some clinical situations and transplantations. Transplantation settings require even greater vigilance in donor selection, blood preparation, and pathogen screening, and may also involve new lifestyle expectations for organ or stem cell donors. An investigation is needed into the hepatitis E virus and vidarabine resistance in these high-risk cohorts of patients. Clinical settings: This concise review highlights a high-risk group for bloodborne infections, their transfusion requirements, and the criteria for transfusion. The most notable topic is arguably a complex and devastating haemoglobinopathy, sickle cell disease (SCD), which necessitates repeated and frequent transfusions for critical reasons, particularly because sickling prevention, splenic function and immune defence are often compromised. Some pathogens, such as parvovirus B19, pose specific risks in SCD. Bone marrow and solid organ transplantation as potential transmission modes during and after transplantation will also be discussed, with a focus on more recent data in various transplant settings.

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Introduction

This brief review will highlight a specifically endangered genetic haemoglobinopathy, namely Sickle Cell Disease (SCD). It is arguably the most serious and complex congenital haemoglobin abnormality. From a clinical perspective, it is characterised by numerous sickled red blood cell clumps, provoked vaso-occlusive signs and crises, along with haematological abnormalities that often require frequent transfusions. In most cases, these conditions are also associated with hypo-asplenic states. This combination necessitates extra efforts to prevent transfusion-transmitted disorders, especially in multitransfused patients with poorly functioning spleens and compromised immune defences. Sickling may be significantly reduced by innovative therapies, mainly based on cell modifications, which will be briefly discussed. However, these approaches may also pose risks of pathogen transmission. Additionally, new data on the Hepatitis E virus in vulnerable patients is presented, with a particular focus on the vidarabine-refractory case therapy after transplants. Updated information on transmissible diseases in bone marrow and organ transplant recipients is also included, whether donor- or transfusion-derived.

A. Sickle Cell Disease (SCD)

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The importance of sickle cell disease (SCD) is often underestimated. It is not limited to sub-Saharan Africa and African Americans but also affects Hispanic communities, as well as a large number of individuals in India, the Middle East, and even Greece. The number of SCD cases is increasing [1–3]. Most cases still occur in sub-Saharan countries, such as Nigeria and the Democratic Republic of the Congo, with a 70% rise in reported cases over the past decade. Undoubtedly, African American populations (approximately 8 million homozygous patients and over 300,000 deaths annually) continue to represent a larger share, living within a healthcare system that is better resourced. However, this also impacts Hispanic communities across the United States, the Caribbean, Brazil, Colombia, and other regions. A growing number of cases are being observed in several Middle Eastern countries. Some cases (0.2-2.7%) have been identified even in Greece, and it is clear that a substantial cohort of patients exists in India as well. The percentage of homozygous cases is similar to that seen in North America, but the population is much larger. Additionally, medical standards vary more widely.

Therefore, a brief overview of the clinical course is necessary, highlighting the significant role of red cell transfusion in patients with hypo- and asplenic conditions. Issues related to bloodborne diseases are of particular concern, particularly regarding infections (such as parvovirus B19 and hepatitis C) or the development of vascular events and bone marrow aplasia [4–7].

The beta-globin gene on chromosome 11 has undergone a mutation, resulting in the production of HbS. This severe condition poses a threat to individuals with homozygous cases, while those with heterozygous cases (sickle cell trait) typically experience minimal symptoms. The oxygen-carrying ability of the mutated haemoglobin in HbS is reduced (similar to other thalassemias). Additionally, red blood cells containing HbS often change shape and can become sickle-shaped (sickling). These sickled cells are too rigid for proper circulation in the microvasculature. Various vaso-occlusive crises may occur when sickling increases (sometimes known, though others are due to not yet fully understood provocative factors). These crises can cause acute pain, stroke, coronary occlusion (even in infants as young as 6 months), and chronic organ damage [7–11].

The survival data for SCD homozygous African Americans is limited; their expected lifespan is relatively low. It is 20-25 years shorter than that of other African Americans. The two main traditional elements of vaso-occlusive event prevention are based on strategies for reducing the proportion of HbS in the blood. These are systemic, repeated courses of hydroxyurea along with frequent, repeated transfusions, and of course protecting antimicrobial immunity or administering such agents [2,5,11,12].

However, some types of innovative, more recent therapy show real promise in terms of lifespan improvement. These include allogeneic transplantation, P-selectin inhibition to block vaso-occlusive events (crisanlisumab) and, most importantly, gene modification of the red blood cells of SCD patients. This achieves better oxygen affinity and avoids sickling, as demonstrated by Lyfgenia and Casgevy [13,14]

These measures may prolong survival and, in the meantime, facilitate an increase in infections, including transfusion-transmitted infections, among polytransfused patients. Still, they may also carry a small risk of pathogen transmission through cell therapy.

Transfusion-Transmitted Disorders in SCD

As previously noted, the social background, haemovigilance, and preparatory measures for blood transfusion in SCD patients vary considerably across different regions. The transmission of the classical quartet (HBV, HCV, HTLV-1, and HIV) was widespread 20-25 years ago. HCV remains a significant concern, with high rates (ranging from 40-60%) still present in less-developed countries. Improvements in blood preparation safety have led to a notable reduction in the incidence of HTLV and HBV, with an approximate 2% decrease observed in most countries involved. However, HCV continues to be an issue. In SCD patients who have undergone numerous transfusions (10 or more), prevalence rates of up to 12% or higher have been reported, indicating a complex underlying cause.

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This includes differences in molecular virus detection levels and genotype shifts of the C virus [15–20].

Patients with SCD who have received more than 10 transfusions seem particularly vulnerable to parvovirus B19 transmission, regardless of the route of infection. In cases of pure red cell aplasia in SCD, where the condition is usually rapid and severe, and rarely treatable or curable, Parvo B19 can also trigger acute vaso-occlusive events. This is a serious condition and, even more concerning, can lead to an acute aplastic bone marrow crisis, involving the destruction of all precursor cell lines. Similar to severe aplastic anaemia. This condition can be fatal and develops quickly. In some cases, treatments such as intravenous immunoglobulins and anti-CD38 monoclonal infusions are not quick enough. Although mortality remains high, treatments such as transfusions, supportive therapies, and Rescue of allogeneic bone marrow transplants might be considered.

Chronic hepatitis B virus (HBV) infection is common among patients with sickle cell disease (SCD), as shown by extensive studies from the United States, with seropositivity for HBsAg ranging from 0 to 3.3 percent. In regions where HBV is more widespread, higher rates of chronic HBV have been observed in patients with SCD compared to the general population. The hepatitis C virus (HCV) has been detected in 10 to 20 percent of patients with SCD [19]. Patients who have received multiple transfusions are at greater risk of infection. In one particular study, the presence of antibodies to HCV was identified more frequently among patients who had received more than 10 units of packed red blood cells (23% versus 8% and 0% in those who had received fewer than 10 units or no transfusions, respectively). Thanks to improved screening techniques, the risk of acquiring HCV through blood transfusions in the US has become very low (about 1 in 1,900,000). In Egypt, twenty-three per cent of patients (16 individuals) tested positive for HCV antibodies; 56.3% of these (9 individuals) had undetectable HCV RNA in their serum, and 43.7% (7 individuals) had persistent viremia.

Hepatitis C virus leads to serious consequences in SCD, including chronic liver disease, increased risk of complications and higher rates of liver cancer compared to non-SCD patients.

The C virus genotypes CC/CT/TT of rs12979860 were detected in 30 (42.9%), 29 (41.4%), and 11 (15.7%) patients, while the rs12980275 AA/AG/GG genotypes were found in 8 (11.4%), 59 (84.3%), and 3 (4.3%) patients. No significant difference was observed in the frequency of IL28B (rs12979860 and rs12980275) genotypes among HCV patients who cleared the virus and those with persistent viremia ($p = 0.308$ and 0.724, respectively). Egyptian SCD patients show a high prevalence of HCV; multi-transfused patients remain at risk of HCV transmission. In this group of Egyptian children with SCD, IL28B gene polymorphisms are not linked to spontaneous HCV clearance. HCV IL28B polymorphism is associated with improved HCV clearance [19]. HCV vaccination effort in China might be considered extremely important; however, the vaccine is not commercially available yet)

SCD patients should be prepared for more severe acute hepatitis symptoms, primarily due to chronic Liver iron overload, likely accompanied by bilirubin-type gallstones and secondary cholecystitis. The presence of extrahepatic manifestations (e.g. proteinuria, cytopenia, neurological signs) is more common and requires specialised care.

Blood Group Alloimmunity in SCD

The clinical observations suggest that the best anti-infection defence is in individuals with blood Group 0+. Although bacterial infections are uncommon, they account for 16% of transfusion-related fatalities. Patients who are iron overloaded like SCD) are particularly susceptible to Yersinia enterocolitica. Red cell alloimmunisation is a serious issue that could potentially affect 50% of transfused patients. However, preventive phenotypic matching for common antigens can reduce alloimmunisation; limited matching for at least E, C, and K has become the standard of care.

Some parallels can be drawn between blood group alloimmunisation and other non-SCD polytransfused cases. In this context, Rh issues are critically important because, unlike in other clinical settings, hemolysis can be more severe and lead to vaso-occlusive episodes. Furthermore, the presence of Rh-specific alloimmunisation can be detected in 5-41% of cases. Simple matching revealed alloimmunisation in 0-5% of cases, while extended matching showed a rate of 0-24%. This is much

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higher than in other patients who have received multiple transfusions. In SCD, immunosuppression appears to be particularly risky, and reducing leukocytes might be a beneficial strategy. [20,21]. Packed red cells are the preferred blood component. Leukocyte-reduced units should be the standard because of their beneficial effects in reducing alloimmunization, transfusion reactions, platelet refractoriness, and the transmission of infections.

Blood group alloantigen positive patients may have impaired immunological defence, some encapsulated, COVID-19. or sometimes Parvo B19 might develop,

B. More Recent Data on the Hepatitis E Virus (HEV)

Approximately 12% of the general population in various countries are HEV IgG positive, and most cases probably remain undetected in Africa. There are eight different genotypes of HEV. The most common phenotypes include HEV 1-4. In Latin America, Africa, and Asia, HEV 1 and 2 are the most prevalent, with the latter two being transmitted through contaminated drinking water. Many mammals are susceptible to infection by HEV 3 and 4, which can be transmitted through contact with undercooked food or via the faecal route [22]. These major HEV genetic variants have further subtypes with different properties. They can react to interferons of types I, II, and III, and they can exhibit antiviral actions during both the acute and chronic phases. The interferon response can be impaired in immunosuppressed patients [24,25].

The hepatitis E genotype is essential in two specific contexts: SCD and certain transplant settings. The 205 participants in the survey included 115 males (56.1%) and 90 females (43.9%). Two or more transfusions were received by 99 (48.8%) of the patients, while 49 (23.9%) had received only one. 57 (27.8%) participants had never had a transfusion. Patients receiving anti CD20therapies are more likely to acquire HEV.

Increasingly, whole-genome sequencing is used to study HEV, and some variants and mutants have been identified as resistant to standard anti-HEV treatments, such as ribavirin. These are sometimes sequence snippets or insertions in the large HEV hypervariable region. (WU). A survey of kidney transplant recipients from Japan revealed that HEV anti-IgG was present in 4.3% of the study participants, while IgM positivity was absent. The results were consistent across all patients. Patients with HEV IgG were slightly older and had received more transfusions before transplant. HEV serology is likely essential in this setting [25].

PEG interferon might be introduced if ribavirin proves ineffective. HEV vaccination (approved in China but not yet available) may also be necessary. Sobosovir combined with ribavirin appears to be a promising option. However, HEV genetic variants A1343V, G1364R, whether alone or combined, may also develop resistance to Sobosovir. These genetic alterations could be part of a response to treatment, even if they are present from the beginning.

In some cases, vidarabine-based antiviral therapy requires extended treatment periods. In cases of relapse, the effectiveness of therapy is reduced; in comparison to the 90 per cent response of healthy populations, SCD and post-transplant cases only respond positively around 40 per cent.[23,24,26]

Organ transplants:

The donor's pre-transplant examination and infection screening are essential whenever a living donor method is used. In cases of brain-death but heartbeating donors, the screening period is limited due to the short cold reperfusion time caused by biological factors, and they remain in intensive care units. If there is an urgent need to transplant a cadaver organ, the cold reperfusion period is even briefer, which prevents sufficient time for thorough pathogen testing. In such situations, it is even more essential to focus on lifestyle factors and consider the threats common to the geographical region and its surrounding areas. Screening of living donors appears to be becoming increasingly important across all transplantation scenarios. Dogs and raccoons (mainly dogs in China) should be screened for active tuberculosis.

Donor screening is already complicated enough, but it could become even more so due to unexpected transmissible diseases and certain lifestyle factors (such as rafting, rock climbing, and close contact with some animals) [27,30,31].

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Trypanosoma cruzi, Strongyloides stercoralis, West Nile virus, Brucella, and rabies, especially if there has been close contact with dogs. In Spain, cases of organ transplant transmission of Leishmania have been reported. Leptospira, along with activities such as agricultural work, rafting, and rock climbing, have also been linked to a silent infection which might be transmissible. Travelling to regions with a high risk of malaria, leishmaniasis, schistosomiasis, or strongyloidiasis increases the risk of infection in patients who have undergone a transplant (bone marrow or organ, depending on the type and level of immunosuppression). [33–35]. Toxoplasmosis is of the greatest concern in Europe, especially in heart and bone marrow transplants (including haploidentical cases). Disseminated cases are often associated with high mortality. Therefore, caution is vital, and transplant teams must remain vigilant. It is also important to note that low-level oncogenic hepatitis B virus variants can persist despite effective anti-HBV prophylaxis in some organ transplant recipients.

Torque teno (TT virus), a potential pathogen, is found more frequently in chronic haemodialysis (17%) and kidney transplant (36%) cases. The TT virus genotype varies, but the clinical courses remain similar. Further studies and close follow-up are necessary to determine the clinical significance of this phenomenon [36,37]. Kidney transplant patients, especially those who do not have HLA-A2, are more likely to experience immune responses against organs from CMV-positive donors due to the virus. These responses are identified by T cells that produce IFN-γ and are specific to the virus. Most of these cases had silent clinical courses, but CMV screening should be carefully considered in organ transplants, based on the recipient's CMV status and the potential for reactivation [32].

It is interesting to note that even a cornea transplant, where blood flow is limited, cannot be considered entirely free from transmission, despite the extremely low likelihood of this occurring. Two cases of HBV and two cases of Creutzfeldt-Jakob disease have been documented. Contact lenses of the donor can increase the transmission of these diseases, and, interestingly, also contribute to the development of neurological and cognitive disorders. It may be advisable not to use corneal tissue from patients who have previously worn contact lenses [38].

There is a growing amount of data on organ or stem cell transplants (as well as other types of cell therapies) and blood-borne infections. These cases, such as arboviruses like dengue, chikungunya, tick-borne encephalitis, WNV, and Zika virus, are transmitted from animals to humans. HEV is a zoonosis, meaning it can cause more severe liver and other health issues, and it can reduce the effectiveness of antiviral treatments, particularly in organ transplant patients. Lymphocytic choriomeningitis and ehrlichiosis should also be taken into account.

Bone marrow transplantation:

Of course, standard viral screening, bacterial, and other pathogen examinations are critical in bone marrow donors; the procedure allows sufficient time for this. The CMV status of the donor and patient is highly significant, even though opinions may not be entirely consistent and vary. Parvovirus B19 screening is also very crucial (pure red cell aplasia).

Hepatitis E virus serology and virus PCR appear to be crucial, including virus genotype analysis if available, and considering geographical differences. Hepatitis E virus may cause more severe hepatitis-like syndrome and chronic disease if transmitted via bone marrow transplant or blood transfusion. Vidarabine-refractory cases are more common in this setting and require careful consultation with a hepatologist on how to proceed. Screening for the hepatitis E virus seems to be a more settled matter. Although vidarabine therapy is usually successful in eradicating persistent viruses, some cases may still relapse. Repeat therapy with vidarabine might be an effective solution. It is crucial to gather more information about how well vidarabine works and how frequently it can be administered to at-risk patients, especially after transplants. However, in cases of post-transplant HEV, repeated vidarabine treatment only works in about half of the patients [26].

Patients receiving bone marrow transplants are more vulnerable to infections caused by Entamoeba histolytica, Cryptosporidium, and Giardia. Reports are also emerging of an increasing number of zoonotic cases.

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Cooled platelet issue:

Red blood cell transfusion is necessary in nearly all bone marrow transplant cases, with the well-known but not excessively high risk of pathogen transmission. Platelet transfusions are given in large quantities and frequently to bone marrow transplant patients, as platelet count recovery is slower after transplant compared to other cell lines (50-100 Units). Platelet transfusion carries a greater risk of pathogen transmission than RBC transfusion, mainly because of the very short incubation time needed to achieve optimal platelet function.

The risk is significantly higher with platelet transfusions, which is a major concern in oncohaematology and bone marrow transplant patient care. The estimated transmission rate of bacterial infections is 1 in 2,000–5,000 units of platelet transfusions from pooled, whole-blood-derived platelets and 1 in 15,000 units from single-donor apheresis preparations. This notable difference mainly results from storing platelet products at room temperature (22 ± 2 °C).

Biological differences: Cooled temperature-prepared platelets are disappearing much quicker from circulation than standard temperature platelets. They bind to glycoprotein receptors, activating clotting. Formation goes quickly, and is more effective in acute bleeding, but less potent in maintaining platelet counts within the required range. Anyhow, pathogen transmission is less with cool prepared platelets. Platelet thawing and in vitro culture are promising approaches to reduce the risk of pathogen transmission, and efforts are underway to preserve their functional activity.

Viral Reactivations Following Bone Marrow Transplantation

Post-bone marrow transplant viral reactivations can lead to two types of serious problems. Type 1: Viral disease is active, causing illness, clinical signs, and potentially leading to critical or severe symptoms. Good examples include reactivation of Cytomegalovirus, BK, RS, and EBV viruses. Type 2: Other viruses can also impair the function of the bone graft or cause graft loss, and may induce GVHD, such as adenovirus, RS virus, parvovirus B19, and cytomegalovirus. These facts underscore the importance of regular monitoring, particularly when clinical signs are present.

Conclusions

Sickle cell disease is a condition that can significantly impact various aspects of health, leading to a wide range of potentially life-threatening complications. These include vascular events, hypo-asplenia, and impaired immune system function. The disease often results in a lower quality of life and a shorter life expectancy for those affected. To manage and prevent vaso-occlusive complications, regular transfusions are essential. There is also an increased risk of:

-multitransfusion

-increased susceptibility to a series of infectious diseases, some of which may be blood-borne

-unusual clinical course (e.g. parvovirus B19, hepatitis E virus)

-The presence of blood group antibodies requires extra caution during serological matching procedures. Particular attention is crucial for blood-borne or other transmitted infections involving traditionally recognised agents, as well as for unusual donor-derived infection risks, according to new data in the presence of some blood group alloantigens.

Organ and bone marrow stem cell transplantation shares transmission risks with many common pathogens, zoonoses, and other unexpected infections. The shorter time of non-living (brain death or cadaver) organ transplantation leaves much shorter times for different in vitro tests. Hence, lifestyle details and geographical differences are even more critical. Hepatitis E virus means a severe problem in all transplanted patients. Cooled platelets are an attractive approach to decrease pathogen transmission through platelet transfusions (especially in large amounts in bone marrow transplant settings). However, many details remain unclear and require more experience. Viral reactivation exhibits similarities, yet profound differences, in patient cohorts undergoing organ or bone marrow transplantation.

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39. Important CMV, EBV, Adeno, RS viralreactivation, maybe lifer threatening, and damages bone marrow, may provoke rejection and influence GVHD.
40. BK virus reactivation is quite common (also in kidney transplanted patients), standard diagnosis and therapy is much more convenient

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