Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company’s public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Infectious complications in neonatal transfusion: Narrative review and personal contribution

Maria Bianchi a,1, Nicoletta Orlando a,1, Caterina Giovanna Valentini a, Patrizia Papacci b,1, Giovanni Vento b,c,2, Luciana Teofili a,d,2,c,1

a Dipartimento di Diagnosi per Immagini, Radioterapia Oncologica ed Ematologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy
b Dipartimento di Scienze della salute della donna, del bambino e di sanità pubblica, Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy
c Sessione di Pediatria, Dipartimento di Scienze della salute della donna, del bambino e di sanità pubblica, Università Cattolica del Sacro Cuore, Roma, Italy
d Sezione di Ematologia, Dipartimento di Scienze Radiologiche ed Ematologiche, Università Cattolica del Sacro Cuore, Roma, Italy

A R T I C L E   I N F O

Keywords:
Neonatal transfusion
Cytomegalovirus
Hepatitis
Bacterial infections

A B S T R A C T

Neonates and prematures are among the most transfused categories of patients. Adverse reactions due to transfusions, such as transfusion-transmitted infections, can affect the rest of their lives. In this systematic review, we revise the literature concerning transfusion-transmitted infection in neonates. We reported case-reports and case-series previously published and we integrated these data with our experience at local neonatal intensive care unit. Moreover, we illustrated strategies for mitigating transfusion-transmitted infections, including donor selection and testing, pathogen inactivation technologies and combined approaches, as for Cytomegalovirus infection, integrating leukoreduction and identification of seronegative donors.

1. Introduction

Neonatal transfusion medicine is a modern discipline presenting many areas of debate. For many aspects, including the indications to transfuse definite blood components (i.e. red blood cell - RBC, platelet, or plasma units), the precise triggers for transfusion, or the strategies to prevent adverse consequences of blood products, there is a great variability across neonatal transfusion guidelines and recommendations from different countries. Noteworthy, neonates, particularly those born before their due date, are among the most transfused categories of patients, and getting a transfusion-transmitted infection can affect the rest of their lives. A wide spectrum of transfusion-transmitted infections are reported in the neonatal setting. Most of them reflected those observed in adult people receiving transfusions, and consisted of transmission of hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV). Nevertheless, for distinct types of pathogens, such as cytomegalovirus (CMV), neonates represent by far the most frequently affected population.

In the first part of this review, we summarize the literature reports on transfusion-transmitted infections in neonates (i.e. infant in their first 28 days of life). In the second part, we describe the data gathered on this issue at our neonatology. Finally, we discuss which specific approaches to prevent transfusion-transmitted infections are currently recommended in the neonatal setting, with particular regard to the CMV infection.

2. Literature review

We performed a systematic search on the databases PubMed using the following queries: “Blood Transfusion”[Mesh] AND “Infant, Newborn”[Mesh] AND “Transfusion Reaction”[Mesh]. We excluded papers reporting non-infectious transfusion reactions, papers reporting data in paediatric population not allowing to extrapolate data on neonates, communications at congresses, duplicated studies and papers not in English. M.B, C.G.V, L.T and N.O independently controlled all references, including observational studies, case report, case series and reviews. Discrepancies were discussed and resolved together. In total, 275 references were identified on May 2020. In the end, 44 papers were

Abbreviations: CMV, cytomegalovirus; GVHD, graft versus host disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IUFT, intrauterine fetal transfusion; PB, peripheral blood.

* Corresponding author at: Istituto di Ematologia, Fondazione Policlinico A. Gemelli IRCCS, I-00168 Roma, Italy.
E-mail address: luciana.teofili@unicatt.it (L. Teofili).

These authors equally contributed to the study as first author.

These authors equally contributed to the study as last author.

https://doi.org/10.1016/j.transci.2020.102951

Available online 16 September 2020
1473-0502/© 2020 Elsevier Ltd. All rights reserved.
3. Five-year experience at our neonatology

Records relative to patients admitted at our neonatology department from January 2014 to December 2019 were revised. At our hospital, blood donor testing does not include CMV serology at donation. Fresh RBC concentrates (≤5 days) destined to neonates are always filtered pre-storage. Plasma units consisted of pharmaceutical grade plasma (Kedrion S.p.A Barga, Italy) since 2013. Platelet transfusions consisted of single units (until January 2016), apheresis units, or pool platelets (from February 2016 onward). Pathogen inactivation started on February 2016, and was performed through Intercept™ Blood System technology (Cerus Europe BV, Amersfoort, Netherlands). RBC and PLT units were subjected to γ-irradiation before to be administered. All neonates were fed with fresh milk from the own mothers, or, if maternal milk was not available, with preterm formula milk. Milk was collected only from mothers with negative IgM serology for toxoplasmosis, rubella virus, CMV, Herpes simplex virus, and varicella-zoster virus.

In total 4268 units (2,626 RBC, 1,192 PLT and 450 PLT units) were distributed to 729 patients. Apart from CMV, no further transfusion-transmitted infections were recorded among our patients. Considering only neonates who had never received maternal milk, CMV TTI occurred in 10 patients (0.9%). All patients were preterm infants: the median gestational age was 27.6 weeks (range 24.0–30.0) and median birth weight 775 g (range 580–1,550). In all CMV-TTI, the diagnosis was made through the DNA virus detection in pharyngeal swabs and urine (10 patients), and bloodstream (5 patients). Each patient received a median number of 5.5 RBC units (range 1–19). Four patients were also given PLT (2 patients) or plasma (2 patients) transfusions. One RhD positive neonate born from a mother with anti-RhD iso-immunization, received from the 19th week of gestation 6 intra-uterine RBC units, and after the birth, additional 5 units. Conceivably, in this case, CMV transmission had occurred in the pre-natal period. In fact, this neonate displayed since her birth a hypo-regenerative anemia unresponsive to erythropoietin, with persistently low reticulocyte count and bilirubin levels, high serum levels of ferritin and soluble transferrin receptor. The CMV infection required treatment in 9 out of 10 cases; 2 patient died for severe bronchopulmonary dysplasia. Three additional cases of CMV infection were observed: neonates were fed with maternal milk and in all cases was documented the CMV presence in the milk.

4. Prevention of transfusion-transmitted infections

Transfusion of blood components is known to carry infectious risks to the recipients. Several actions can be put in place to prevent infections such as careful donor selection and deferral, leukoreduction, implementation of testing and pathogen inactivation.

Donor selection and consequent deferral for high-risk donors represents the first-line option in preventing infections. For infections such Hepatitis B, C, HIV and syphilis candidate donors undergo a careful evaluation of sexual behavior, high-risk activities (piercing, tattoo, etc.) or antibiotic treatment (surgery, endoscopy, etc.). Travelling information may add useful information to reduce the risk of transmission of infection in donors from endemic area (i.e. malaria, Chagas’ disease) or in case of seasonal outbreaks (i.e. Dengue, Chikungunya, West Nile Virus, etc.). Moreover, donors are asked about signs of recent infections such as gastrointestinal symptoms (which is a risk factor for Yersinia species contamination), recent fever and/or respiratory symptoms (for influenza virus, Coronavirus, etc.) or antibiotic treatment [31]. In addition, at the time of collection, health professionals must carefully inspect donor skin to avoid venipuncture in scared skin and, most important, perform diversion of the initial blood (from 10 to 30 mL) after venipuncture, in a satellite pouch, to avoid bacterial
CMV infection in neonates undergoing blood transfusions. Legend. BW, birth weight; CMV, Cytomegalovirus; ET, exchange transfusion; RBC, red blood cell; VLBWI, very low birth weight infant.

| Reference          | Population | Patients (n)/blood components | CMV status of the mothers | Results                                                                 | Comments                                                                 |
|--------------------|------------|-------------------------------|---------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Nankervis          | Newborns   | 24/ET                         | All mothers were tested but data were not reported | 21 % (5/24) were infected with CMV an 6–12 weeks after birth:  - One of 5 received blood from seronegative donor  - 4 received blood from seropositive donors  | Transplacental antibodies were not protective.                            |
| Spector et al.     | Prematures | Total enrolled 93: 93/blood transfusion 14/ET | NA                        | 13/93 with cytomegaloviruria  All received blood from a mean of 10.45 different donors (only 5 underwent ET) 80/93 without cytomegaloviruria All received blood from a mean of 5.10 different donors (only 9 underwent ET) 8 babies became infected:  - 4 after blood transfusions not showing clinical signs of infection;  - 4 after ET: 3 showed no clinical signs attributable to CMV, 1 died. | No clinical data were reported. No clinical data were reported. The number of transfusions was significantly higher in positive patients (p < 0.002). Human milk was used in only two patients: one of these was not frozen |
| Preiksaitis et al. | Infants    | Retrospectively 42: 32/blood 16/ET | NA                        | 16 babies who received only CMV seronegative blood remained unaffected. | Blood donor CMV status has an impact on the probability to be infected from CMV |
| Kumar et al.       | Newborns   | Total enrolled 355: 353/RBC 221 seronegative donors | Mothers were screened but data are not reported | Four babies had CMV from urine and throat after 6–12 weeks after transfusion. Three of these had transplacental antibody to CMV  One infant became infected. She received blood from two donors: one seronegative, the other with unknown serological status. Ten of the 74 infants who were exposed to CMV seropositive donors become infected. | Blood from seropositive or unknown donors has a higher risk to transmit CMV. In case newborns with transplacental antibody, these seem not to be protective. |
| Yeager et al.      | Prematures | Total enrolled 355: 353/RBC 221 seronegative donors | Mothers were screened but data are not reported | 164 seronegative mothers  Four of the 10 infected infants had fatal infection or died from chronic lung disease. One infant had serious complications. All of these 5 had <28 weeks and <1200 g of weight. Nine of the 60 infants who were exposed to CMV seropositive donors become infected. Twenty-three of 131 infants who were exposed to CMV seronegative donors become infected. None had fatal infection or serious complications. | In prematures, there is a higher risk to be infected from CMV when receiving blood from seropositive donors. Maternal antibodies do not prevent CMV transmission. None of the babies received fresh milk from his/her mother. |
| Adler et al.       | Newborns   | 178/RBC                       | Mothers were screened but data are not reported | Eight newborns acquired CMV infection during their hospital stay. Seven of these have a seronegative mother. Six infants who acquired CMV infection developed morbidity associated with this infection, three of them died. Only one of 126 seronegative infants (114 from phase A and 12 from phase B) developed CMV infection. Only one of 16 seropositive infants developed CMV infection. No mortality and very little morbidity were attributed to transfusion acquired CMV infection. | Significant correlation between the number of different blood donors from whom an infant received blood and CMV infection (p < 0.0001) No infant was fed nonmaternal breast milk. |
| Preiksaitis et al. | Newborns   | Phase A: all infant 114 RBC (no ultrafiltrated, washed or irradiated) platelets 28 RBC (no ultrafiltrated, washed or irradiated) platelets | Seronegative mothers | Eight infants acquired CMV:  - Phase 1: 7 were transfused with blood from one or more ELISA-positive donors and from one or more IgM-positive donors.  - Phase 2: 1 received negative blood for CMV IgM but positive at Elisa test performed later. Two of the eight seropositive donors developed characteristic symptoms. One of these infants died of respiratory distress. Eight infants acquired CMV:  - Phase 1: 7 were transfused with blood from one or more ELISA-positive donors and from one or more IgM-positive donors.  - Phase 2: 1 received negative blood for CMV IgM but positive at Elisa test performed later. Two of the eight seropositive donors developed characteristic symptoms. One of these infants died of respiratory distress. Eight infants acquired CMV:  - Phase 1: 7 were transfused with blood from one or more ELISA-positive donors and from one or more IgM-positive donors.  - Phase 2: 1 received negative blood for CMV IgM but positive at Elisa test performed later. Two of the eight seropositive donors developed characteristic symptoms. One of these infants died of respiratory distress. Eight infants acquired CMV:  - Phase 1: 7 were transfused with blood from one or more ELISA-positive donors and from one or more IgM-positive donors.  - Phase 2: 1 received negative blood for CMV IgM but positive at Elisa test performed later. Two of the eight seropositive donors developed characteristic symptoms. One of these infants died of respiratory distress. | Infants rarely received more than two transfusion from any one donor. All infants received only maternal or sterilized donated breast milk. |
| Lambersen et al.   | Infants    | Phase B: infant with BW < 1,250g 549/RBC CMV serological assay were performed retrospectively | NA                        | Eight infants acquired CMV:  - Phase 1: 7 were transfused with blood from one or more ELISA-positive donors and from one or more IgM-positive donors.  - Phase 2: 1 received negative blood for CMV IgM but positive at Elisa test performed later. Two of the eight seropositive donors developed characteristic symptoms. One of these infants died of respiratory distress. Eight infants acquired CMV:  - Phase 1: 7 were transfused with blood from one or more ELISA-positive donors and from one or more IgM-positive donors.  - Phase 2: 1 received negative blood for CMV IgM but positive at Elisa test performed later. Two of the eight seropositive donors developed characteristic symptoms. One of these infants died of respiratory distress. Eight infants acquired CMV:  - Phase 1: 7 were transfused with blood from one or more ELISA-positive donors and from one or more IgM-positive donors.  - Phase 2: 1 received negative blood for CMV IgM but positive at Elisa test performed later. Two of the eight seropositive donors developed characteristic symptoms. One of these infants died of respiratory distress. | Most infected neonates received multiple transfusions, however an infants received only a small volume of blood from a donor. Screening donors for CMV IgM was effective to reducing transfusion associated-CMV. |
| Bhumin et al.      | Newborns   | 137/RBC 13/fresh frozen plasma | All mothers were seronegative | One infant acquired CMV infection through granulocyte transfusions. Neither infant had any symptoms attributable to CMV infection. | The use of seronegative red blood cell is highly successful in the prevention of primary CMV infection. |

(continued on next page)
contamination, especially Gram-positive organisms [32].

Leukoreduction is the reduction of white blood cell (WBC) concentration in blood components, RBCs, platelet concentrates and plasma obtained from the fractionation of whole blood or apheresis. There are many methods of LR but, currently, this process may be performed using selective last-generation LR filters, which allow obtaining less than one million residual WBCs in an RBC or PC unit. Over the past thirty years, it has been demonstrated that LR can reduce some adverse reactions due to blood component transfusion such as febrile non-hemolytic transfusion reactions, immunization against HLA and HPA antigens, which may cause refractoriness to platelet transfusion, and transmission of CMV [33,34]. Some early studies demonstrated that both policies, namely the use of CMV seronegative blood components and LR, may be able to determine a significant reduction of CMV infection in high-risk patients. However, controversies concerning “the gold standard” practice (only LR, only CMV-donor status, and LR plus CMV-donor status) are still ongoing [35–37].

Nowadays, infections still represent a great risk but the epidemiology of TTI is changed over the years. The introduction of NAT testing (Nucleic Acid Amplification) for HIV, HBV and HCV had significantly lowered the residual risk of 1:1 million to 1:10 million, while risk for bacterial contamination is still high (1:2,000–1:5,000) in platelet concentrates, with a high rate of fatal sepsis (10 %) [38]. Underestimation of these phenomena may be also due to clusters of patients receiving platelet concentrates. Adult and pediatric patients with onc-hematological diseases as well as premature who easily present sepsis, comorbidities and immune system deficits during the course of their disease often received several platelet transfusions from different donors [38].

In the last years, an important strategy to minimize the risk of TTI is pathogen reduction technologies. These are effective on several well-known viruses as well emerging viruses, bacteria and protozoa. Different technologies have been developed for acellular (plasma) and cellular blood components (platelet concentrates). Acellular blood components may be inactivated with solvent-detergent (SD) for plasma pool or with methylene blue (MB) for single plasma units. SD plasma is generally performed by pharmaceutical industries using tri(n-butyl) phosphate and octonanol for 1–1.5 h at +30 °C. The main limitation of this method is the lack of efficiency on envelope-free viruses such as Parvovirus B19, Hepatitis A and E. This limit is overcome with additional testing on donors. MB plasma is not indicated for pediatric patients since adverse events were reported, as well as interference with phototherapy treatment [39,40]. SD or MB method cannot be used for pathogen-inactivation technologies are able to inactivate a wide range of Gram positive and negative bacteria (4.5 to 6.9 log reduction) and negative bacteria (4.5 to 6.9 log reduction) without compromising platelet functions and reducing residual leukocytes in blood components (INTERCEPT™) as well as they are active on slow-growing bacteria (Mirasol® and Siroflex®) [42].

Pathogen-reduction technologies are promising in preventing bacterial infections where molecular and/or culture-based method may be ineffective. As previously described, bacterial contamination in blood components is the most frequent TTI and platelet concentrates are the principal blood components involved, mainly due to their storage conditions (20–24 °C). Gram-positive bacteria (i.e. Staphylococcus epidermidis, Staphylococcus aureus) are often involved and they normally are part of the skin flora. Gram-negative bacteria are rare and mainly due to asymptomatic bacteremia in blood donors, after red blood cell transfusions or use of blood cell-saver during surgeries [47]. Pathogen inactivation technologies are able to inactivate a wide range of Gram positive (from 3.6 to >6.9 log reduction) and negative bacteria (4.5 to >6.7 log reduction) without compromising platelet functions and reducing residual leukocytes in blood components (INTERCEPT™) as well as they are active on slow-growing bacteria (Mirasol®) [42].

In terms of safety, some studies reported experiences in pediatric patients. Platelet concentrates treated with INTERCEPT™ system were successfully transfused in 46 neonates (less than 28 days) without any adverse events. Mirasol-platelet concentrates were transfused in 51 children showing no difference in the rate of adverse events when compared to patients no-receiving Mirasol-platelet concentrates. For THERAFLEX® the only concern is on the use of MB in neonates, which can determine, as already described, adverse events [41]. Notwithstanding the efficacy of leukoreduction in removing residual white blood cells, viral transmission from blood components remains at

Table 1 (continued)

| Reference | Population | Patients (±)/blood components | CMV status of the mothers | Results | Comments |
|-----------|------------|--------------------------------|--------------------------|---------|----------|
| Galea et al. [10] | Newborns with BW < 1,500g | 83/RBC and fresh frozen plasma | NA | Seven of 83 (8.4 %) infants became infected with CMV in all transfused population. No clinical data were reported. | Incidence of CMV infection was only present (7/70, 10 %) in newborns receiving blood from seropositive donors. |
| de Cates et al. [11] | Prematures ≤32 weeks | Part 1: 53 | Mothers were screened but data are not reported for all babies | 10/53 (19 %) infants acquired CMV infection (three of them had seronegative mothers and seven had seropositive mothers). One patient died at two months of age 6/72 (8.3 %) infants acquired CMV infection (three of them had seronegative mothers and three had seropositive mothers) | Preterms babies should be transfused with seronegative CMV blood regardless the serological status of the mother. |
| Kim et al. [12] | Newborns with BW < 1500g | Part 2: 75 | 80/filtered, irradiated RBC and platelets | No clinical data were reported, 2/80 (2.5 %) acquired CMV infection None received breast milk | The use of filtered and irradiated do not differ from the use of no-filtered, no-irradiated RBC and platelets (p > 0.05) in hyperemdidemic area. |
risk for CMV and donations from CMV sero-positive donors may represent a risk for nonimmune patients.

5. What CMV-safe does mean?

CMV is a worldwide endemic herpesvirus and the prevalence of CMV seronegative individuals varies according age, country and ethnicity [48]. For example, a French study on general people reported a prevalence of 42 % for CMV-IgG antibodies among individuals aged 15–49, with a higher frequency in females than in males [48]. A German study carried out among blood donors showed a seroprevalence of 30 % for those aged 18–30, and of 80 % for those older than 65 years, with female donors having a 15 % higher risk at all ages [50]. Regarding ethnicity, a British study carried out among pregnant females showed a CMV seroprevalence of 49 % among White British women, of 89 % among South Asian UK born women and of 98 % among South Asian women born in South Asia [51].

During the primary infection, CMV replication occurs in several cells including myeloid cells, and is followed by an IgM response. Therefore, viral transmission can occur if the donor is in the window phase [52]. After the primary infection, CMV persists lifelong latent in leukocytes. Viral transmission can occur if the donor is in the window phase [52].

Table 2
Microbial TTI in neonates undergoing blood transfusions. Legend. BW, birth weight; ET, exchange transfusion; RBC, red blood cell.

| Reference             | Population  | Patients (n)/Product transfused | Pathogen  | Outcome |
|-----------------------|-------------|---------------------------------|-----------|---------|
| Seeberg et al. [17]   | Infant      | 1/ET with blood from four different donors | HAV       | A female baby was the source of the outbreak in a pediatric surgical ward. TTI is associated with a period of viremia and viremia of 25 days before the onset of jaundice. One blood donor was responsible for HAV transmission and he was identified one month after donation. |
| Ammann et al. [18]    | Infant      | 1/6 ET, 5 platelets and 7 partial ET from eighteen donors in the first 2 weeks of life | HIV       | Eighteen months after birth HIV infection was diagnosed. The child died at 2 years of age because of P. carinii pneumonia. |
| Noble et al. [19]     | Neonates    | 2/RBC and fresh frozen plasma   | HAV       | One male donor donated blood and this was transfused to 11 neonates (pedi-pack units). Later, he developed symptomatic HAV. Two neonates had HAV following blood transfusion from this donor. Two patient were infected by blood transfusion from a IgM anti-HAV positive donor. The donor was a male who developed clinical symptoms some days after donation. Only after HAV diagnosis, he revealed a sexual intercourse with a male not tested. |
| Azimi et al. [20]     | Prematures  | 2/RBC from 26 donors            | HAV       | The donor could not be traced. |
| O’Riordan et al. [21] | Infant      | 20/RBC, platelets               | HCV       | 11/20 (55 %) presented HCV serological testing positive and only 5 had positive molecular testing (genotype 1b). All of the reported children are clinically asymptomatic. Six donors were identified: 1 viremic mother who performed direct donation to her child; 5 donors who were infected following anti-D administration (4) or not specified other source (1). The index case was one of the three children receiving one aliquot of plasma. The other two neonates died within some days from transfusion. The donor was a female with a negative medical history, but his boyfriend was diagnosed with HAV shortly after her donation. |
| Lee et al. [22]       | Infant      | 3/Plasma unit was divided into three aliquots assigned to three different patients | HAV       | Identification of index case was performed following outbreaks among personnel in a NICU. |
| Vareil et al. [23]    | Newborn     | 1/whole blood                   | P. falciparum | The patient received a 60-mL whole blood transfusion in Senegal. The chronology of events and exposure to blood are highly suggestive of transfusion-transmitted malaria. |
| Hervaldt et al. [24]  | Prematures  | 13/RBC or platelets             | Babesia microti | From 1997–2009, 13 transfusion-associated Babesia cases occurred in the United States. Most cases were associated with RBC transfusion while 2 to whole blood-derived platelets. |
| Simonsen et al. [25]  | Prematures  | 7/RBC                           | Babesia microti | Transfusion from 2 infected units of blood resulted in 7 cases of neonatal transfusion-associated babesiosis. The extremely low birth weight neonates were the most severely affected. Double-volume exchange blood transfusion with prolonged multidrug treatment was required for 2 most severe cases. |
| Martini et al. [26]   | Newborn      | 1/platelets                     | S. epidermidis | Female newborn underwent platelets transfusion. Six hours after, she developed fever (39.8 °C). She died of septic shock the same days. Three received aliquots from the same unit: 2 had HAV infection and the third had no HBV markers. |
| Niederhauser et al. [27]| Newborn   | 3/RBC                           | HBV         | Blood donor was negative for HBsAg and not tested for anti-Hbc or HBV DNA. Blood donor was negative for HBsAg and not tested for anti-Hbc or HBV DNA. The donor was a male who developed clinical symptoms some days after donation. |
| Waldenstrom et al. [28]| Newborn    | 1/RBC                           | HCV         | A 9-day old neonate received two RBC units from two different donors during surgery. HCV infection in one donor was identified 29 days after transfusion in plasma sent to industries for pharmaceutical products. |
| Van Schalkmyk et al. [29]| Neonates | 48/blood                        | Candida krusei | A large outbreak of Candida krusei candidemia in a neonatal unit occurring during 4 months. The source of this outbreak could not be established, however blood transfusion were identified as a risk factor in Candidemia positive infants. Four infants were transfused with the same packed RBC from a donor unknowingly infected with Babesia microti. Two of the infants developed high-grade of parasitemia. |
| Glanternik et al. [30]| Newborn     | 4/RBC                           | Babesia microti | |

5. What CMV-safe does mean?

CMV is a worldwide endemic herpesvirus and the prevalence of CMV seronegative individuals varies according age, country and ethnicity [48]. For example, a French study on general people reported a prevalence of 42 % for CMV-IgG antibodies among individuals aged 15–49, with a higher frequency in females than in males [48]. A German study carried out among blood donors showed a seroprevalence of 30 % for those aged 18–30, and of 80 % for those older than 65 years, with female donors having a 15 % higher risk at all ages [50]. Regarding ethnicity, a British study carried out among pregnant females showed a CMV seroprevalence of 49 % among White British women, of 89 % among South Asian UK born women and of 98 % among South Asian women born in South Asia [51].

During the primary infection, CMV replication occurs in several cells including myeloid cells, and is followed by an IgM response. Therefore, viral transmission can occur if the donor is in the window phase [52]. After the primary infection, CMV persists lifelong latent in leukocytes. Either the reactivation of a latent infection or the re-infection by a different strain can occur, accompanied by viral shedding in body fluids, including milk and blood. Indeed, CMV can be transmitted by blood donated in all these circumstances. Basically, CMV-seronegative patients undergoing hematopoietic stem cell transplant (HSCT) from seronegative donors and preterm neonates are the patient populations carrying the highest risk for transfusion-transmitted CMV infection. Blood
components obtained from IgG/IgM seronegative donors could prevent CMV transmission in exchange-transfused neonates [53]. Indeed, seronegative blood products became the standard to prevent CMV transmission in patients at risk. Since CMV is mainly present in white blood cells, the modern filters for leukodepletion have significantly reduced this risk in cellular products, dropping from 10 to 59 % of fresh blood to 3 % or less in leukodepleted products [48]. In 1995, a study of Bowden et al. in HSCT patients, found that leukodepleted blood products reduced the day-21 risk for CMV infection/disease to a similar extent as using blood from CMV-seronegative donors [36]. At a secondary analysis, CMV transmission in exchange-transfused neonates [53]. Indeed, sero.

[36] Laverdanta EL, Bodoia S, Bodoia J. Cytomegalovirus in neonates acquired by blood transfusions. Pediatr Infect Dis 1983;2(3):114–8. May–Apr.

[37] Prikakis J, Brown L, McKenzie M. Transfusion-acquired cytomegalovirus infection in neonates. A prospective study. Transfusion 1988;28(3):205–9. May–Jun.

[38] Lambertson Jr HV, McMillan JA, Weiner LB, et al. Prevention of transfusion-associated cytomegalovirus (CMV) infection in neonates by screening blood donors for IgM to CMV. J Infect Dis 1988;157(4):820–3.

[39] Bhumbra NA, Leavandowsky P, Lau P, Sererer M, Satiah M, Nankervis GA. Evaluation of a prescreening blood donor program for prevention of perinatal transmission-acquired cytomegalovirus (CMV) infection. J Perinat Med 1988;16(2):127–31.

[40] Galea G, Urbananik SJ. The incidence and consequences of cytomegalovirus transmission via blood transfusion to low birth weight, premature infants in north east Scotland. Vox Sang 1992;62(6):400–7.

[41] de Cates CR, Gray J, Roberton NR, Walker J. Acquisition of cytomegalovirus infection by premature neonates. J Infect 1994;28(1):25–30. Jan.

[42] Kim AR, Lee YK, Kim KA, Cho KY, Baik KY, Kim ES, et al. Transfusion-related cytomegalovirus infection among very low birth weight infants in an endemic area. J Korean Med Sci 2006;21(1):5–10. Feb.

[43] Adler SP, Lawrence LT, Baggert J, Bivo V, Sharp DE. Prevention of transfusion-associated cytomegalovirus infection in very low birth-weight infants using frozen blood and donors seronegative for cytomegalovirus. Transfusion 1984;24(4):333–5. Jul–Aug.

[44] Taylor BJ, Jacobs RF, Baker RL, Moses EB, McSwain BE, Shulman G. Frozen deglycerolized blood products prevent transfusion-acquired cytomegalovirus infections in neonates. Pediatr Infect Dis 1986;5(2):188–91.

[45] Demmler GJ, Brady MT, Bivui H, Speer ME, Milam JD, Hawkins EP, et al. Posttransfusion cytomegalovirus infection in neonates: role of saline-washed red blood cells. J Pediatr 1986;108(5 Pt 1):137–6. May.

[46] Luban NL, Williams AE, Macdonald MG, Mikelsen GT, Williams KM, Sacher RA. Low incidence of acquired cytomegalovirus infection in neonates transfused with washed red blood cells. Am J Dis Child 1987;141(4):416–9. Apr.

[47] Seiberg SG, Brandenburg A, Hermodson S, Larsen P, Lundgren S. Hospital outbreak of hepatitis A secondary to blood exchange in a baby Lancet 1981;1(8230):1155–6. May 23.

[48] Ammann AJ, Cowan MJ, Wara DW, Weintrub P, Dritz S, Goldman H, et al. Acquired immunodeficiency in an infant: possible transmission by means of blood products. Lancet 1983;1(8331):956–8. Apr 30.

[49] Noble RC, Kana MA, Reeves SA, Roekeiél L. Posttransfusion hepatitis A in a neonatal intensive care unit. JAMA 1984;252(19):2711–5. Nov 16.

[50] Azimi PH, Roberts RO, Gurlinek J, Livermore T, Hoag S, Hagemann S, et al. Transfusion-acquired hepatitis A in a premature infant with secondary nosocomial spread in an intensive care nursery. Am J Dis Child 1986;140(1):23–7. Jan.

[51] O’Riordan JM, Couray A, Nourse C, Yap LF, McDonald GS, Kamiński G, et al. Risk of hepatitis C infection in neonates transfused with blood from donors infected with hepatitis C. Transfus Med 1998;8(4):303–8. Dec.

[52] Lee KK, Vargo LR, Le CT, Fernando L. Transfusion-acquired hepatitis A outbreak from fresh frozen plasma in a neonatal intensive care unit. Pediatr Infect Dis J 1992;11(2):122–3. Feb.

[53] Varel MO, Tandonnet O, Chemoul A, Bogreau H, Saint-Léger M, Micheau M, et al. Unusual transmission of Plasmodium falciaporcs, Bordeaux, France, 2009. Emerg Infect Dis. 2011;17(2):258–60. Feb 19.

[54] Herwaldt BL, Linden JV, Bosserman E, Young C, Olkowska D, Wilson M. Posttransfusion hepatitis A in a neonatal intensive care unit. JAMA 1984;252(19):2711–5. Nov 16.

[55] Simonson KA, Harwell BJ, Laiwala S. Clinical presentation and treatment of transfusion-associated hepatitis in premature infants. Pediatrics 2011;128(4):e1019–24. Oct.

[56] Martini R, Roniker R, Rodrigues M, Andermeier B, Mekenna MM, Kutzaff V. Bacteriological analysis of patients and cases of septicaemia associated with transfusion of contaminated samples. Transfus Apher Sci 2012;47(3):313–8. Dec.

[57] Niederhauser C, Cantodi D, Weingand T, Maier A, Tinguely C, Stolz M, et al. Reverse vertical transmission of hepatitis B virus (HBV) infection from a transfusion-infected newborn to her mother. J Hepatol 2012;56(1):73–7. Mar.

[58] Waldenstrom J, Konar J, Ekermo B, Norder H, Lagging M. Neonatal transfusion-transmitted hepatitis C virus infection following a per-seroconversion window-phase donation in Sweden. Scand J Infect Dis 2013;45(10):796–9. Oct 18.

[59] van Schalkwyk E, Ido S, Naicker SD, Maphang TGC, Mpmbe RB, Zulu TG, et al. Large outbreaks of fungal and bacterial bloodstream infections in a neonatal unit, South Africa, 2012–2016. Emerg Infect Dis 2018;24(7):1204–12. Jul.

[60] Glanternik JR, Baine IL, Rychalsky MR, Tormey CA, Shapiro ED, Baltimore RS. Transfusion and Apheresis Science 59 (2020) 102951

6

[61] Planteur JM, Baine I, Rychalsky M, Tormey C, Shapiro E, Baltimore R. A cluster traced to a single unit of donor blood. Pediatr Infect Dis J 2018:37(3):269–71. Mar.

[62] Grossman BJ, Collins P, Lau PM, Perretten JL, Bowman RJ, Malcolm S, et al. Screening blood donors for gastrointestinal illness: a strategy to eliminate carriers of Yersinia enterocolitica. Transfusion 1991;31(6):500. Oct.

[63] de Korte D, Curvers J, de Kort WL, Hoekstra E, van der Poel CL, Beckers EA, et al. Effects of skin disinfection method, deviation bag, and bacterial screening on clinical safety of platelet transfusions in the Netherlands. Transfusion 2006;46(3):475–85. Mar.
[33] Ferguson D, Khanna MP, Timmout A, Hebert PC. Transfusion of leukoreduced red blood cells may decrease postoperative infections: two meta-analyses of randomized controlled trials. Can J Anaesth 2004;51:417–24.

[34] Blumberg N, Zhao H, Wang H, Messi S, Heal JM, Lyman GH. The intention-to-treat principle in clinical trials and meta-analyses of leukoreduced blood transfusions in surgical patients. Transfusion 2007;47(4):573–81. Apr.

[35] Blajchman MA, Goldman M, Freedman JJ, Sher GD. Proceedings of a consensus conference: prevention of post-transfusion CMV in the era of universal leukoreduction. Transfus Med Rev 2001;15:1–20.

[36] Bowden RA, Slichter SJ, Sayers M, Weisdorf D, Cays M, Schoh G, et al. A comparison of filtered leukocyte-reduced and cytomegalovirus (CMV) seronegative blood products for the prevention of transfusion-associated CMV infection after marrow transplant. Blood 1995;86(9):598–603. Nov 1.

[37] Nichols WG, Price TH, Gooley T, Corey L, Boeckh M. Transfusion-transmitted cytomegalovirus infection after receipt of leukoreduced blood products. Blood 2003;101(10):4195–200. May 15.

[38] Schlenke P. Pathogen inactivation technologies for cellular blood components: an update. Transfus Med Hemother 2014;41(4):309–25.

[39] Porat R, Magilner D, Metheny blue-induced phototoxicity: an unrecognized complication. Pediatrics 1996;97(5):717–21.

[40] Sills MR, Zinkham WH. Methylen blue-induced Heinz body hemolytic anemia. Arch Pediatr Adolesc Med 1994;148(3):306–10.

[41] Jacquot C, Delaney M. Pathogen-inactivated blood products for pediatric patients: blood safety, patient safety, or both? Transfusion 2018;58(9):2095–101.

[42] Levy JH, Neal MD, Herman JH. Bacterial contamination of platelets for transfusion: strategies for prevention. Crit Care 2018;22(1):271.

[43] Rasonyol P, Angelini-Tibert MF, Isola H, Kientz D, et al. Transfusion of platelet components prepared with photochemical pathogen inactivation treatment during a Chikungunya virus epidemic in Ile de La Réunion. Transfusion 2009;49(6):1083.

[44] Mohr H, Kniver-Hopf J, Gravemann U, Boeckh M. Transfusion-transmitted cytomegalovirus infection associated with leucodepleted blood components. Vox Sang 2015;109(1):11–21.

[45] Ziemann M, Heuft HG, Frank K, Krasn S, Gorg S, Hessig H. Window period donations during primary cytomegalovirus infection and risk of transfusion-transmitted infections. Transfusion 2013;53(5):1088–94.

[46] Luthardt T, Siebert H, Losel I, Quevedo M, Tordt R. Cytomegalovirus-infektion bei Kindern mit Blutautstauschtransfusion im Neugeborenenalter (Cytomegalovirus infections in infants with blood exchange transfusions after birth). Klin Wochenschr 1971;49(2):81–6.

[47] Fergusson D, Khanna MP, Heshi Y, Uchida S, Suzuki K, Tadokoro K. Cytomegalovirus (CMV) seroprevalence in Japanese blood donors and high detection frequency of CMV DNA in elderly donors. Transfusion 2013;53(10):2190–7.

[48] Josephson CD, Caliendo AM, Esley KA, Knezevic A, Shenvi N, Hinkef MS, et al. Blood transfusion and breast milk transmission of cytomegalovirus in very low birth-weight infants: a prospective cohort study. JAMA Pediatr 2014;168(11):1054–62. Nov.

[49] Seed CR, Wong J, Polizzotto MN, Faddy H, Keller AJ, Pink J. The residual risk of transfusion-transmitted cytomegalovirus infection associated with leucodepleted blood components. Vox Sang 2015;109(1):11–7.

[50] Delaney M, Mayock D, Knezevic A, Norby-Slycord C, Peter R, et al. Postnatal cytomegalovirus infection: a pilot comparative effectiveness study of transfusion safety using leukoreduced-only transfusion strategy. Transfusion 2016;56(8):1945–50. Aug.

[51] Parkers RI. Transfusion in critically ill children: indications, risks, and challenges. Crit Care Med 2014;42(3):675–90.

[52] Ziemann M, Thiele T. Transfusion-transmitted CMV infection - current knowledge and future perspectives. Transfus Med 2017;27(4):238–48.

[53] Antona D, Lepoutre A, Fonteneau L, Baudon C, Halfenheimer-Zhou F, LESTRAT Y, et al. Seroprevalence of cytomegalovirus infection in France in 2010. Epidemiol Infect 2017;145(7):1471–8. May.

[54] Hecker M, Qiu D, Marquardt K, Bein G, Hackstein H. Continuous cytomegalovirus seroconversion in a large group of healthy blood donors. Vox Sang 2004;86(1):41–4.

[55] Pembrey L, Raynor P, Griffiths P, Chaytor S, Wright J, Hall AJ. Seroprevalence of cytomegalovirus, Epstein Barr virus and varicella zoster virus among pregnant women in Bradford: a cohort study. PLoS One 2013;8(11):e81881.

[56] Ziemann M, Heufk HG, Frank K, Krasn S, Gorg S, Hessig H. Window period distributions during primary cytomegalovirus infection and risk of transfusion-transmitted infections. Transfusion 2013;53(5):1088–94.

[57] Ziemann M, Thiele T. Transfusion-transmitted cytomegalovirus infection associated with leucodepleted blood components. Vox Sang 2015;109(1):11–7.

[58] Eickmann M, Gravemann U, Handke W, Tolksdf F, Reichenberg S, Müller TH, et al. Transfusion-transmitted cytomegalovirus infection associated with leucodepleted blood components. Vox Sang 2015;109(1):11–7.

[59] Delany M, Mayock D, Knezevic A, Norby-Slycord C, Peter R, et al. Postnatal cytomegalovirus infection: a pilot comparative effectiveness study of transfusion safety using leukoreduced-only transfusion strategy. Transfusion 2016;56(8):1945–50. Aug.

[60] Vanmackes EC. Is white blood cell reduction equivalent to antibody screening in preventing transmission of cytomegalovirus by transfusion? A review of the literature and meta-analysis. Transfus Med Rev 2005;19(3):181–99.

[61] Caprati MG, Lanari M, Lazzarotto T, Gabrieli I, Pignatelli S, Corvaglia L, et al. Very low birth weight infants born to cytomegalovirus-seropositive mothers fed with their mother’s milk: a prospective study. J Pediatr 2009;154(6):842–8. Jun.