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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,c}, Giovanni Vento^{b,c,2}, Luciana Teofili^{a,d,2,*}

^a Dipartimento di Diagnostica 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 Sezione 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

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ABSTRACT

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 revised 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).

¹ These authors equally contributed to the study as first author.

² These authors equally contributed to the study as last author.

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included and discussed in the review (Fig. 1). In Tables 1 and 2 we summarized case-reports and case-series of TTI from 1976 to 2018.

In Table 1, we reported CMV infection in neonates undergoing blood transfusions in a wide range of years with different transfusion practices [1–12]. Transfusions and viral shedding in the milk of seropositive mothers are the two main routes implicated in transmitting post-natal CMV infection. Several papers showed that blood components from CMV-seropositive donors are potentially the major cause of CMV infections in neonates. Testing CMV status of the donor is the most effective strategy in preventing transfusion-associated CMV infection [3–5,8–11]. Moreover, exposing neonates to a low number of donors may be also preventive [2,6,8]. Only one paper reported different data but, in this study, infants rarely received more than two transfusions [7]. The role of passive maternal antibody transmission seems to be not protective in preventing CMV infection [1,4]. Some authors proposed blood components treatments to prevent CMV transmission. In the 80', we reviewed experiences dealing with RBC freezing in a glycerol medium [13,14] and washing to remove leukocyte [15,16]. These methods may be considered obsolete. In fact, frozen RBCs need additional technologies, they are expensive and not based on a cost-effectiveness analysis. Washing to remove leukocyte may be easily overcome with last-generation leukoreduction filters.

In Table 2, we reported TTI due to different etiological agents [17–30]. For hepatitis A, post-transfusion transmission was confirmed in all cases and index patients were also responsible to spread HAV through fecal-oral via causing nosocomial infection in other patients, their parents and personnel [17,19,20,22]. For Hepatitis B and C, asymptomatic or untested donors (i.e. NAT testing not yet available) were responsible for transmission [21,27,28]. Only one TTI HIV infection was reported and it happened at the beginning of the 80's [18]. Some microbes are

mainly transmitted by some blood components such as RBC (malaria parasites, Babesia) or platelet concentrates (bacteria) [23–26,29,18–30].

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, CVM 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 medical interventions (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 scarred skin and, most important, perform diversion of the initial blood (from 10 to 30 mL) after venipuncture, in a satellite pouch, to avoid bacterial

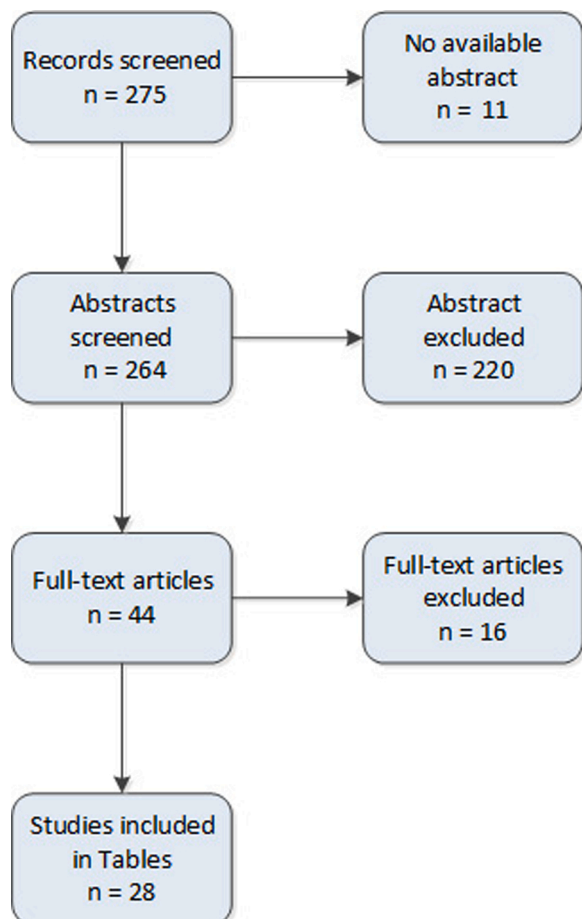


Fig. 1. Study flow diagram.

Table 1

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 [1]	Newborns	24/ET	All mothers were tested but not data were reported	21 % (5/24) were infected with CMV at 6–12 weeks after birth: - One of 5 received blood from seronegative donor - 4 received blood from seropositive donors No clinical disease was detected in this population.	Transplacental antibodies were not protective.
Spector et al. [2]	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. The number of transfusions was significant higher in positive patients ($p < 0.002$). Human milk was used in only two patients: one of these was not frozen
Benson et al. [3]	Infants	Retrospectively 42: 32/blood 16/ET untested blood Prospectively 22: 14/blood 2/ET Seronegative donors 29/ET	NA	16 babies who received only CMV seronegative blood remained uninfected.	Blood donor CMV status has an impact on the probability to be infected from CMV
Kumar et al. [4]	Newborns	Group 1: patients receiving blood from seropositive blood donors (n = 15) Group 2: patients receiving blood from seronegative blood donors (n = 14)	Mothers were screened but data are not reported 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. Four of the 10 infected infants had fatal infection or died from chronic lung disease. One infants 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. 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. 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 seronegative infants developed characteristic symptoms. One of these infants died of respiratory distress. Two infants developed CMV infection and viruria after each received CMV seropositive blood (these units were mistakenly identified as CMV seronegative due to technical errors or poor sensitivity of the test kit). One infant acquired CMV infection through granulocyte transfusions. Neither infant had any symptoms attributable to CMV infection.	Blood from seropositive or unknown donors has a higher risk to transmit CMV. In case newborns with transplacental antibody, these seem not be protective. 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. 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.
Yeager et al. [5]	Prematures	Total enrolled 355: 353/RBC 134 seropositive donors 221 seronegative donors	164 seronegative mothers 191 seropositive mothers		
Adler et al. [6]	Newborns	178/RBC	Mothers were screened but data are not reported		
Preiksaitis et al. [7]	Phase A: all infant Phase B: infant with BW < 1,250g	114 RBC (no ultrafiltrated, washed or irradiated) platelets 28 RBC (no ultrafiltrated, washed or irradiated) platelets Phase 1: 549 /RBC CMV serological assay were performed retrospectively	Seronegative mothers Seronegative (12) and seropositive (16) mothers NA		Infants rarely received more than two transfusion from any one donor. All infants received only maternal or sterilized donated breast milk.
Lamberson et al. [8]	Infants	Phase 2: 439 /RBC, CMV IgM was performed on the day of donation: only CMV IgM negative donors were used.	NA		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.
Bhumbra et al. [9]	Newborns with BW < 2,000g	Total enrolled 137: 137/RBC 13/fresh frozen plasma Not specified/granulocyte At beginning, all donors were seronegative but 16 (0.7 %) seroconverted during the study.	All mothers were seronegative		The use of seronegative red blood cell is highly successful in the prevention of primary CMV infection.

(continued on next page)

Table 1 (continued)

Reference	Population	Patients (n)/blood components	CMV status of the mothers	Results	Comments
Galea et al. [10]	Newborns with BW < 1,500g	83/RBC and fresh frozen plasma 70 exposed to seropositive blood components	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 Part 2: 75	Mothers were screened but data are not reported for all babies 26 had seropositive mothers, 49 had seronegative mothers.	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) No clinical data were reported, 2/80 (2.5 %) acquired CMV infection None received breast milk	Preterms babies should be transfused with seronegative CMV blood regardless the serological status of the mother.
Kim et al. [12]	Newborns with BW < 1500g	80/filtered, irradiated RBC and platelets 20/no-filtered, no-irradiated RBC and platelets All donors were screened for CMV	NA	2/20 (10 %) acquired CMV infection. One received frozen 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 hyperendemic area.

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 onco-hematological diseases as well as prematures 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 octynol 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 cellular blood components because may be responsible for cellular damages with a consequent effect on transfusion efficacy and risks of

adverse events.

For cellular blood components different technologies have been developed mainly based on UV light and addition of photosensitive compounds. At the moment three technologies are available: INTERCEPT™ (Cerus Corporation, USA), Mirasol® (Terumo BCT, USA) and THERAFLEX® (Macopharma, France) [38,41,42]. INTERCEPT™ is a CE-marked and FDA-approved device for plasma and platelets concentrates using amatosalen, which intercalates between DNA bases; after UVA exposure, there is an inhibition of transcription and cellular reproduction. Mirasol® is a CE-marked device using riboflavin and UVB light, while THERAFLEX® has different technologies for plasma, where MB is used, and only UVC light for platelets, which induces the formation of pyrimidine dimers and prevents DNA replication. In addition to well-known viruses (HIV, HBV, HCV and HTLV), these technologies may be used for preventing transmission of emerging infections affecting world population in the last decades. Pathogen-inactivation technologies have found a wide application in preventing transmission of Chikungunya Virus during outbreaks in La Reunion, West Nile Virus, Zika virus and Coronavirus (SARS) in addition to NAT testing, when available [43–46].

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. Platelets 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 effects [41].

Notwithstanding the efficacy of leukoreduction in removing residual white blood cells, viral transmission from blood components remains at

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	Patogen	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 two years of age because of <i>P. carinii</i> pneumonia. One of the platelet donors was identified as a patient with AIDS who had died 17 months after blood donation.
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.
Azimi et al. [20]	Prematures	2/RBC from 26 donors	HAV	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.
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).
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. 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 her boyfriend was diagnosed with HAV shortly after her donation.
Vareil et al. [23]	Newborn	1/whole blood	<i>P. falciparum</i>	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. The donor not could be traced.
Herwaldt et al. [24]	Prematures and full-term infant	13/RBC or platelets	<i>Babesia microti</i>	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 (<32 week of gestational age)	7/RBC	<i>Babesia microti</i>	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	<i>S. epidermidis</i>	Female newborn underwent platelets transfusion. Six hours after, she developed fever (39.8 °C). She died of septic shock the same days.
Niederhauser et al. [27]	Newborns	3/RBC	HBV	Three received aliquots from the same unit: 2 had HBV infection and the third had no HBV markers. Blood donor was negative for HBsAg and not tested for anti-HBc or HBV DNA.
Waldenström et al. [28]	Newborn (9-day old age)	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	<i>Candida krusei</i>	A large outbreak of <i>Candida krusei</i> 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.
Glanternik et al. [30]	Newborn	4/RBC	<i>Babesia microti</i>	Four infants were transfused with the same packed RBC from a donor unknowingly infected with <i>Babesia microti</i> . Two of the infants developed high-grade of parasitemia.

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 [49]. 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 carried out at post-transplant day 100, however, there were fewer CMV infection and disease in the seronegative arm [36]. At present, it is unknown if testing CMV DNA can further reduce the risk for CMV transmission of leukodepleted blood products. Noteworthy, among 2400 blood donor samples serially collected at 10-year intervals, CMV DNA was found in 4.3 % of samples from donors in their 60 s and in 1.0 % of samples from donors younger than 60 years, whereas none of the 562 seronegative samples was found DNA positive [54].

Maternal milk transmission seems to be the main responsible for post-natal CMV infection if CMV-seronegative and leukoreduced blood products are used. In a seminal study on 2061 CMV-seronegative and leukoreduced transfusions to 310 neonates, none of postnatal CMV infection was linked to transfusion, whereas all 28 infants with CMV infection were fed with maternal breast milk from CMV-seropositive mothers [55]. Although theoretically estimated below the threshold of 1 in 1 million [56], the residual CMV-transmission risk in leukodepleted products has never been evaluated in randomized or even large case-control neonate populations, but only in a pilot study including 20 neonates [57]. In 2005, a meta-analysis of controlled studies available at that time in HSCT patients, indicated that CMV-seronegative blood components are more efficacious than leukodepleted blood components in preventing transfusion-acquired CMV infection [58]. Similarly, our data gathered in neonates not receiving maternal milk suggest that leukoreduction alone might be not sufficient to defeat the risk for transfusion-transmitted CMV infection in fetuses or neonates. Notably, at variance with CMV infection transmitted by fresh maternal milk, which is mild and self-limiting in the majority of patients, 9 out of 10 patients in our series required antiviral therapy [59].

6. Conclusions

The numerous reports on transfusion-transmitted infections in newborn recipients in the past literature clearly show that blood donor testing has made over years blood neonatal transfusion progressively safer. The implementation of pathogen inactivation in plasma and platelet units further protects patients from non-screened infectious agents. Unfortunately, however, no similar methodologies are so far available for RBC concentrates. Our data clearly show that transfusion-transmitted CMV infection in premature neonates is still a concern in neonatal care units. In this context, an evidence-based clear equivalence of leukoreduced to seronegative-donor cellular products is still lacking, even for fetal and neonatal transfusions.

Declaration of Competing Interest

The authors report no declarations of interest.

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