

Response to Reviewers

We would like to thank and appreciate of your valuable comments and paper review. Our responses are hereby presented as follows:

Comment 1:

Maybe it would be useful to compose a summary table listing the virus type, its known prevalence in UCB together with so far reported cases of UCB transplant related infection (where available).

Reply:

As suggested by the reviewer, the summary of the viral pathogens and the reports of post-UCBT viral infection either primary infection or reactivation in the manuscript is presented in the table with their references. (at the end of the revised manuscript)

Furthermore, the previously reported cases of UCB-transplanted patients who developed the virus-related disorders from graft-cell origin were considered within the manuscript (highlighted in yellow in the revised manuscript)

Comment 2:

Is there a geographical worldwide distribution of the contamination risk accordingly the virus type?

Reply:

Currently, there is no reported geographical distribution of the contamination risk, according to the virus type. Nonetheless, very limited reports mentioned about the correlation between the source of graft and the pattern of viral infections. For example, it has been shown that HHV-6 infections were more frequently observed after umbilical cord blood transplantation than after unrelated peripheral blood stem cell (PBSC) in adults, while no correlation could be established for CMV or EBV (1-5).

- 1- **Chevallier P**, Hebia-Fellah I, Planche L, Guillaume T, Bressollette-Bodin C, Coste-Burel M, Fanny R, Mohty M, Imbert-Marcille BM. Human herpes virus 6 infection is a hallmark of cord blood transplant in adults and may participate to delayed engraftment: a comparison with matched unrelated donors as stem cell source, Bone Marrow Transplant 2010 ;45(7):1204-11 [PMID: 19935727 DOI: 10.1038/bmt.2009.326]
- 2- **Yamane A**, Mori T, Suzuki S, Mihara A, Yamazaki R, Aisa Y, Nakazato T, Shimizu T, Ikeda Y, Okamoto S. Risk Factors for Developing Human Herpesvirus 6 (HHV-6) Reactivation after Allogeneic Hematopoietic Stem Cell Transplantation and Its

Association with Central Nervous System Disorders. *Biol. Blood Marrow Transplant* 2007;13(1):100-106 [PMID: 17222758 DOI: 10.1016/j.bbmt.2006.09.003]

- 3- **Scheurer ME**, Pritchett JC, Amirian ES, Zemke NR, Lusso P, Ljungman P. HHV-6 encephalitis in umbilical cord blood transplantation: A systematic review and meta-analysis. *Bone Marrow Transplant* 2013;48(4):574-580 [PMID: 23000642 DOI:10.1038/bmt.2012.180]
- 4- **Hill JA**, Koo S, Guzman Suarez BB, Ho VT, Cutler C, Koreth J, Armand P, Alyea EP, Baden LR, Antin JH, Soiffer RJ, Marty FM. Cord-Blood Hematopoietic Stem Cell Transplant Confers an Increased Risk for Human Herpesvirus-6-Associated Acute Limbic Encephalitis: A Cohort Analysis. *Biol. Blood Marrow Transplant* 2012;18(11):1638-1648 [PMID: 22564265 DOI: 10.1016/j.bbmt.2012.04.016]

Comment 3:

It would be really important the authors based on their expertise, give more details about practical modalities of screening UCB donors for viral transmission.

Reply:

Currently, screening UCB units for transmissible infectious diseases (HIV, HTLV, HBV, HCV, CMV, and syphilis) is performed in two general ways by public cord blood banks including the mother screening before or after delivery, and testing the UCB units.

Maternal samples are evaluated by serologic method and nucleic acid testing (NAT) [1].

Testing UCB units for transmissible infectious diseases is a reliable approach as recommended by NetCord-FACT, but there is not any FDA-approved diagnostic kit for specific testing on UCB units, until now [2]. Therefore, screening strategy is the same as that used for blood donors [3]. Considering viral infections as the potential threats to the hematopoietic stem cell transplantation safety, additional strategies for the prevention, careful screening and follow-up, and preemptive therapy are necessary in any transplantation center.

- 1- Guidance to Accompany the NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration, Fourth Edition. 2010. (<http://www.scribd.com/doc/62168694/4thEditionCordBloodGuidance4-0>) Accessed: 1 June 2012.
- 2- NetCord-FACT International Standards for Cord Blood Collection, Banking and Release for Administration: sixth edition. 2015. (http://www.factwebsite.org/uploadedFiles/Standards/NetCord%20FACT%206th%20Ed%20Standards%20Draft.09.01.15_Redlined.pdf). Accessed: 12 July 2017.
- 3- Armson BA; Maternal/Fetal Medicine Committee, Society of Obstetricians and Gynaecologists of Canada. Umbilical cord blood banking: implications for perinatal care providers. *J Obstet Gynaecol Can* 2005; 27: 263-290.

Comment 4:

Finally, as there were mentioned in the abstract, the importance and eventual reported (if any_) cases of viral contamination with UCB derived cell therapies would be welcome.

Reply:

As suggested by the reviewer, the previously reported cases of UCB-transplanted patients who developed the virus-related disorders from graft-cell origin were considered within the manuscript (highlighted in yellow in the revised manuscript)