Use of Convalescent Whole Blood or Plasma Collected from Patients Recovered from Ebola Virus Disease for Transfusion, as an Empirical Treatment during Outbreaks

Interim Guidance for National Health Authorities and Blood Transfusion Services

Version 1.0 September 2014

World Health Organization

WHO/HIS/SDS/2014.8

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1 Introduction

While there is no proven treatment available for Ebola virus disease (EVD), whole blood collected from patients in the convalescent phase of infection has been used as an empirical treatment with promising results in a small group of EVD cases.[1] During the current ongoing EVD outbreak, whole blood and plasma collected from EVD recovered patients has been prioritized for investigation, as one of the treatment modalities.[2] The concept that this treatment could be efficacious is biologically plausible, as convalescent plasma has been used successfully for the treatment of a variety of infectious agents.[3]

This interim guidance to national health authorities and blood transfusion services outlines the steps required to collect convalescent whole blood (CWB) or plasma (CP) from EVD recovered patients for transfusion to patients with early EVD, as an empirical treatment modality. It covers:

- The identification of patients recovered from EVD as potential blood donors;
- informed consent and selection of donors;
- donor's blood grouping and screening for transfusion transmissible infections (TTI);
- blood collection and donor care;
- labelling, storage and data collection in blood transfusion services (BTS);
- informed consent of EVD patients;
- patient's blood grouping and compatibility testing;
- storage and transportation of CWB/CP to the sites where transfusions is to be given;
- selection of EVD patients for this intervention;
- the clinical transfusion process;
- data collection at the transfusion site; and
- assessment of the effectiveness of this empirical treatment.

The convalescent WB or plasma should be collected, prepared, stored and transfused in facilities capable of implementing the guidance provided in this document. If the transfusions are planned to be given in a field situation, the *WHO Checklist for essential items for blood transfusion in emergency settings* can provide a useful source of additional information.[4]

This interim guidance will be updated as further evidence and experience accumulates.

2 Guidance on donor selection, screening, donation and handling of blood and plasma units

2.1 Identification of suitable blood or plasma donors among patients recovered from EVD

[1] Mupapa K, Massamba M, Kibadi K, Kuvula K, Bwaka A, Kipasa M, Colebunders R, Muyembe-Tamfum JJ.. Treatment of Ebola hemorrhagic fever with blood transfusions from convalescent patients. International Scientific and Technical Committee. J Infect Dis 179 Suppl 1:S18-23, 1999.

[2] Statement on the WHO Consultation on potential Ebola therapies and vaccines http://www.who.int/mediacentre/news/statements/2014/ebola-therapies-consultation/en/

[3] Luke TC, Casadevall A, Watowich SJ, Hoffman SL, Beigel JH, Burgess TH. Hark back: Passive immunotherapy for influenza and other serious infections. Crit Care Med. 2010 Apr;38(4 Suppl):e66-73.

[4] WHO Checklist for essential items for blood transfusion in emergency settings http://www.who.int/entity/bloodsafety/transfusion_services/essential-items_bts.pdf?ua=1

Patients who have recovered from EVD and who have been discharged from Ebola treatment centres or units could be potential donors for CWB/CP, from 28 days after their day of discharge. Ebola neutralizing antibodies are expected to be most effective when CWB/CP is sourced from the areas of on-going active Ebola virus (EBOV) transmission. However, in circumstances where the demand is high and the system is challenged by an overwhelming number of active EVD patients, CWB/CP could also be sourced from the places linked to the current EVD outbreak in West Africa where the outbreak has come under control.

A register or database of patients recovered from EVD as potential CWB/CP donors should be created. Only those EVD patients who have been discharged according to the WHO criteria as: 1) clinically asymptomatic and 2) twice tested negative for EBOV RNA by molecular techniques, should be considered as potential donors. The two samples for EBOV RNA testing should be taken at least 48 hours apart, and the test results should be negative on each sample. Discharge records of EVD recovered patients should be reviewed before considering them as potential CWB/CP donors.

The donor selection criteria used in the country should be reviewed in light of the potentially life-saving impact of these specific donations. An appropriate risk assessment should be done to assess the risk reduction value of each selection criteria against the risk impact of exclusion of the donor. Where the risk to the donor or the patient is seen to be significantly lower than the risk of non-treatment, consideration should be given to relaxing the donor selection criteria for these specific types of donation. For example, if the current age for blood donation in the country is 18-60 years, and there are significant numbers of EVD recovered patients outside this age range, the national health authorities and BTS may consider relaxing the donor selection criteria to widen the potential donor pool.

Given relaxed criteria, recovered patients who are less than the recommended lower age limit for blood donation may donate blood with parental consent following a thorough medical assessment, including an assessment of total blood volume to determine the acceptable volume to be collected (≤15% of total blood volume for whole blood). Depending on the weight or total blood volume of the potential donor, blood may be collected in small volume (200 mL) blood collection bags. Those above the upper age limit for blood donation should also be assessed by a physician for their suitability to donate. While certain donor selection criteria could be relaxed, the donors selected for donation should be RNA negative for EBOLA and for the transfusion transmissible infections listed in Section 2.3.

2.2 Donor information, consent and selection

When an EVD recovered patient has been identified as a potential donor, the need for collecting his/her whole blood or plasma donation should be explained, emphasizing that this could be useful as an empirical treatment for the EVD patients. Potential donors should be informed that there will be no payment to them for their blood or plasma donation.

In the event that the potential donor agrees to be considered for CWB/CP donation, he/she should be assessed for suitability to donate blood or plasma through a donor selection process, including general health criteria such as weight, medical and social (i.e. behavioural risk factors) history, basic physical examination and haemoglobin estimation.[5]

[5] WHO Guidelines on blood donor selection http://www.who.int/bloodsafety/publications/guide_selection_assessing_suitability.pdf

BTS staff should then obtain written informed consent (Annex 1) from the potential donor for donation of a unit of whole blood or plasma for transfusion. Donor confidentiality should be maintained to avoid any coercion to donate from the community.

2.3 Donor's blood grouping and TTI screening

Potential donors who meet the WHO criteria of recovery from EVD (see section 1) and who also meet the donor selection criteria identified above and have given informed consent should then be subjected to pre-donation testing to assess final suitability for donation, according to the national policy and routine procedures.

Pre-donation testing should include:

- ABO and RhD grouping
- Blood screening tests for HIV, HBV, HCV, syphilis and other locally transmitted infections, as applicable
- Haemoglobin estimation (unless performed as part of the initial donor selection process
- Where possible, titration of total Ebola antibodies and Ebola neutralizing antibodies could also help in the qualification of the donor, particularly if the donor is willing to continue serving as CWB/CP source.

Depending on the test to be performed and the assay system used, either serum or plasma could be used for these tests. Two blood samples of five mL each should be collected for these tests, one in EDTA for a plasma sample and the other one in a plain tube (without anticoagulant) for a serum sample. Residual serum from these blood samples should be stored in aliquots for retrospective antibody testing or any other tests, as required.

2.4 Blood collection and donor care

The results of the pre-donation testing should be reviewed. Potential donors who test negative for all TTI tests and meet all other criteria of donor suitability should be selected for CWD/CP donations. In the event that the time between the pre-donation testing and the donation exceeds 48 hours then the routine TTI testing should be repeated at the time of donation.

Whole blood donation should be collected in a single blood collection bag or if feasible, in a double blood collection bag for the separation of plasma from the red cells by sedimentation or centrifugation. Where possible CP could also be collected by apheresis procedure from suitable donors. Plasmapheresis will enable collection and storage of large volumes of CP that may be used for more than one patient.

The donor should be provided with good care before, during and after the whole blood or plasma donation procedure. Any adverse donor reactions should be adequately and promptly managed and recorded. The *WHO Guidelines on drawing blood: Best practices in phlebotomy* may provide a useful source of information.[6]

[6] WHO Guidelines on drawing blood: Best practices in phlebotomy
http://whqlibdoc.who.int/publications/2010/9789241599221_eng.pdf?ua=1

A minimum period of 12 weeks for males and 16 weeks for females should occur before a further whole blood donation is collected. The inter-donation interval for collection of plasma by apheresis should be two weeks. The minimum interval before a plasmapheresis donation should be four weeks following a whole blood donation or a failed return of red cells during apheresis.

Potential donors with abnormal TTI test results should be referred to appropriate health-care institutions for further investigation, confirmation, counselling, treatment and care.[7]

2.5 Storage of whole blood and plasma units, inventory management and transportation

Donated CWB should be stored between $+2^0$C and $+6^0$C (never frozen) preferably in a separate blood bank refrigerator dedicated to CWB/CP units, fitted with a temperature monitoring system and alarm. In case a separate refrigerator is not available, consideration should be given to storing these units on a separate, labelled shelf within the refrigerator. The storage duration will depend on the anticoagulant and preservative solution in the blood collection bag and must strictly follow manufacturer's instructions. It may be stored up to 35 days if collected in citrate phosphate dextrose with added adenine (CPDA-1). Appropriate labelling should be done to clearly identify CWB/CP units.

CP separated from whole blood donations or collected by apheresis may be stored as 'Liquid Plasma' between $+2^0$C and $+6^0$C in blood bank refrigerators for up to 40 days. Alternatively, it may be frozen either within 8 hours of collection as 'Fresh Frozen Plasma' or within 18-24 hours of collection as 'Plasma Frozen Within 24 hours' and stored for up to 12 months at or below -18^0C in a controlled plasma freezer.[8]

Where there are no facilities to prepare CP by centrifugation, it could be separated from CWB collected in double bags. A CWB unit can be stored vertically for 24 hours between $+2^0$C and $+6^0$C, the supernatant plasma can then be transferred into the secondary bag, and stored as liquid plasma.

Careful inventory management procedures should be in place for these CWB/CP donations collected, with full consideration of ABO and RhD blood groups and age of the CWB/CP units, to minimize loss due to expiry. The CWB/CP units should be transported in temperature controlled conditions.

Considerations shall be given to the need for extended storage of unused expired CWB/CP, to make them available for research purposes.

3 Guidance on transfusion of convalescent whole blood or plasma

3.1 Selection of EVD patients

Only patients with confirmed EVD[9], preferably in its early stages, should be considered for CWB/CP transfusion, as an empirical treatment for EVD.

[7] WHO/CDC/IFRC implementation guidelines: Blood donor counselling http://www.who.int/bloodsafety/voluntary_donation/Blooddonorcounselling.pdf?ua=1

[8] WHO Manual on the management, maintenance and use of blood cold chain equipment http://www.who.int/entity/bloodsafety/Manual_on_Management,Maintenance_and_Use_of_Blood_Cold_Chain_Equipment.pdf?ua=1

[9] Case definition recommendations for Ebola or Marburg Virus Diseases http://www.who.int/csr/resources/publications/ebola/ebola-case-definition-contact-en.pdf?ua=1

3.2 Informed consent

If feasible, informed consent for transfusion of CWB/CP should be obtained from the EVD patient or the family members (Annex 2).

3.3 Collection of patient's blood samples for laboratory testing

The patient should be correctly identified. Two venous blood samples of 5 mL each should be collected from the patient prior to transfusion; one in EDTA for a plasma sample and the other one in a plain tube (without anticoagulant) for a serum sample. These samples are for (a) ABO and RhD blood grouping and cross-matching and (b) for baseline viral load assay.

One 5mL sample should be taken in a plain tube (without anticoagulant) for a serum sample on the day after transfusion to measure viral load and for any other tests, as required.

Prior to discharge of patients that recover, two additional 5 mL samples (each in a plain tube without anticoagulant) are required on consecutive days for viral load measurements. Residual serum from these blood samples should be stored in aliquots for retrospective antibody testing or any other tests, as required.

3.4 Selection of convalescent whole blood or plasma units for transfusion

ABO and RhD matched blood or plasma units should be selected for transfusion. RhD negative units should be used for transfusion to RhD negative women of child-bearing age, if feasible. If the RhD group of the patient is not known or in case of non-availability of RhD specific group, blood matched only for ABO group may be used.

To reduce the risk associated with handling infectious blood samples, cross matching of patients' serum and donors' red cells, may be omitted if ABO group compatible CWB/CP is selected.

When it is not possible to test the patient's ABO group or if ABO matched CWB/CP is not available then:

- For whole blood transfusion: Group O convalescent whole blood, ideally from donors with low titre anti-A and anti-B, should be used;
- For plasma transfusion: Group AB convalescent plasma separated by centrifugation should be used.
    - Non ABO-matched CP separated by centrifugation could also be considered if group AB plasma is not available, but should preferably be group A or group