

Considerations of the WHO Blood Regulators Network (BRN)

*Potential for Use of Convalescent Plasma in Management of Ebola**

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Potential for Use of Convalescent Plasma in Management of Ebola

- Basic principles
- Pros and cons
- Need for controlled studies
- Position paper of the WHO BRN
- WHO consultation on a clinical protocol

Basic Principles

- Primary concerns for Ebola are:
 - Containment (isolation, possible vaccination)
 - Supportive care to patients
- Use of investigational therapies (MoAb, antiviral drugs, convalescent plasma) should not interfere with containment and supportive care strategies, and thus necessitates special considerations
- Local decisions are needed based on urgency, feasibility and best use of resources

Arguments in Favor of Convalescent Plasma for Management of Ebola

- Serum therapies have an extensive history of successful use in certain settings (e.g. diphtheria, pneumococcal pneumonia, anthrax, etc.) and remain important treatments for some conditions (e.g. CMV, parvovirus B19, Argentine Hemorrhagic Fever, etc.).
- Anecdotal evidence (Muppa, et al. J Inf Dis 1999) and some animal studies (Dye, et al. PNAS 2012) suggest possible efficacy of convalescent plasma in Ebola.
- MoAbs are effective in animal models, but may be less available and more costly than transfusion therapy.

Arguments Against Convalescent Plasma in Management of Ebola

- Efforts to establish infrastructures for safe blood collection and use could divert resources from supportive care or other therapies.
- Plasma separation and storage are not always possible based on infrastructures in outbreak areas and might not be sustainable.
- May only have the potential to help those with less advanced disease.
- MoAb might be more effective.

Nevertheless, infrastructures for collection of blood do exist, and transfusion already is an adjunctive therapy for hypovolemic, coagulopathic and hemorrhagic conditions in affected regions. Whole blood could provide single unit equivalent plasma if found effective.

Need for Controlled Studies

- Empirical use of blood is happening already, but its effectiveness is uncertain.
- Urgent investment in blood system infrastructures (at the expense of other interventions) is warranted only if convalescent plasma is known to be effective.
- If effective,
 - convalescent plasma could become more available locally, but the ability to treat large numbers of patients may be limited,
 - there is longer term potential to make a specific immune globulin.

WHO BRN Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Filovirus Outbreak Response

- http://www.who.int/bloodproducts/brn/brn_positionpaperconvplasmafiloviruses_finalweb14august2014.pdf
 - **Motivation to consider convalescent plasma**
 - **Overview of potential for effectiveness of antibodies**
 - **Background on pathogenesis of filovirus infections; human and animal experience with use of antibodies**
 - **Considerations on collection and use**
 - **Role of regulatory agencies**
 - **Regulatory considerations**
 - **Summary**

BRN Paper: Collection and Use of Convalescent Plasma or Serum - I

- Role of regulatory agencies to:
 - Consider the ethical, scientific, logistical and resource issues for use of convalescent plasma
 - Establish and assure standards for safe blood collection and appropriate clinical use
 - Support responsible scientific studies of Ebola specific plasma preparations

BRN Paper: Collection and Use of Convalescent Plasma or Serum - II

- Donors should be qualified based on good health post convalescence from Ebola
- Blood collection and processing should be consistent with well-recognized GMP standards including quality assured testing for HIV, HCV, HBV and syphilis and blood group compatibility testing
- Donors should be negative for Ebola RNA and positive for Ebola neutralizing anti-glycoprotein antibodies performed in qualified laboratories
- Product collections and use should be regarded as experimental, requiring donor and recipient informed consent

BRN Paper: Collection and Use of Convalescent Plasma or Serum - III

- Pathogen reduction
 - to address window period risks of antibody negative donations; other infectious risks of transfusion, e.g. malaria
- Patient selection to maximize therapeutic benefits
 - Use early in the clinical course (prior to coagulopathy and organ failure)
- Sound design of a statistically powered and controlled trial
- Standardized consent and Case Report Forms

WHO Consultation on Protocol Development for Investigational Studies and Clinical Use (Ongoing)

- A controlled study is needed, however
- Feasibility assessments are required first:
 - Ability to locate and recruit donors sufficient to meet study size requirements for confident determination of a predetermined minimum treatment effect
 - Safety of collection, product preparation and storage
 - Quality assured laboratory testing including for Ebola
 - Ethical conduct of a trial including general security
 - Funding and sustainability

Next Steps (per WHO consultation)

- Identify cooperating parties willing to intervene in outbreak areas
- Establish feasibility of a controlled trial
 - Possibility for laboratory testing and apheresis outside of the outbreak area, e.g. in a nearby unaffected country
 - Agreement on a study design
 - Simplified consent process (e.g. scripted medical conversation and basic affirmation)
 - Defined end-points and statistical plan

Summary

- Transfusion with blood from convalescent patients has been used empirically as Ebola therapy with unknown effectiveness.
- Well-designed studies of convalescent plasma could result in criteria for clinical use, but significant assessment of feasibility to carry out a clinical trial is needed as a first step.
- If effective, investment in blood program infrastructures may be warranted as an element of strategies to respond to the current and potentially future outbreaks.