WHO Blood Regulators Network (BRN)

Position Paper on Use of Convalescent Plasma, Serum or Immune Globulin Concentrates as an Element in Response to an Emerging Virus*

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1. Rationale for consideration of use of convalescent plasma or serum

1.1 Overview

Addressing a rapidly emerging virus epidemic associated with high morbidity or mortality can become an urgent local, regional or global public health priority. Based on the concept of passive immunization supported by historical experience, the general possibility exists that application of whole blood, plasma, serum or immune globulin concentrates obtained from convalescent persons might be effective in disease treatment or prevention. Plasma (and indirectly also serum) may be obtained by plasmapheresis which is estimated less stressful for the donor. For this reason, it is prudent to consider the use of convalescent plasma or serum as a potential addition to other measures of preparedness for and response to such epidemics. There is a high likelihood in a rapidly expanding outbreak of a viral disease that large populations of susceptible persons will become ill especially early in the event, prior to availability of effective vaccines and antiviral therapies. An organized program to collect convalescent plasma or serum from disease survivors could provide a potentially valuable empirical intervention while data on effectiveness and safety of its use are obtained through orderly scientific studies. A decision whether to pursue this option requires a rapid, but thorough, review of the knowledge base for the etiologic agent or related agents and the immune response to them in order to assess the likely benefits and risks of passive immunization in the specific epidemic. However, establishment of the infrastructure needed to make this candidate intervention feasible can be developed in advance of an epidemic as part of epidemic preparedness.

1.2 Background

Serum therapies were successfully used to treat many infectious diseases (anthrax, plague, scarlet fever, measles, tularemia, diphtheria, dysentery, meningococcal meningitis, rabies, pneumococcal pneumonia) for half a century after Emil von Behring first demonstrated their effective use as a therapeutic in diphtheria. Their use declined significantly after the advent of antibiotics. However, human and animal derived immunoglobulins remain important therapies for a variety of viral infectious diseases (parvovirus, CMV, hepatitis B, rabies, hepatitis A, etc.) Additionally, there is precedent in the modern era for effective management of Argentine Hemorrhagic Fever (Junin Virus) with convalescent immune plasma as part of a nationally organized response (1).
In a particular virus epidemic, the potential efficacy of convalescent plasma or serum will depend on the extent to which antibodies generated during recovery of the donor would directly neutralize a virus or otherwise mediate an effective immune response. Additionally, questions arise regarding the effective therapeutic dose and whether it can be delivered from conventional units of plasma or serum. Preparation of an immune globulin concentrate might be necessary in order to obtain a mixture of polyclonal antibodies representing different individual donors and a higher antibody concentration. Preliminary information relevant to these issues may be available from previous experience with empirical human use, or by extrapolation from studies done in animal models. The availability and feasibility of assays useful to select donations likely to be therapeutic, e.g. based on high titer of a total or neutralizing antibody, is another relevant consideration. Attention also is needed to the question whether transfusion of convalescent plasma might be harmful based on the risk of unintended transmission of undetected infectious agents present in the donor. Moreover, immune enhancement due to transferred antibodies might exacerbate the disease. Because survivors may harbor other transmissible endemic diseases, it is important that convalescent plasma or serum should be produced using pathogen inactivation and reduction technologies. Where feasible and enough time to prepare, concentrated immunoglobulin preparations may be preferred over single individual plasma units, based on their likelihood of higher potency and greater consistency. These issues need to be considered by the relevant regulatory authority in considering whether to permit scientific studies and empirical use of convalescent plasma or serum to go forward in the epidemic setting. The recent experience with empirical and investigational use of convalescent plasma (and whole blood) in the 2014-2105 outbreak of Ebola virus in West Africa demonstrated that based on an organized and well-considered approach, these products can be collected from willing donors with recent infection, used safely, and assessed scientifically even in the most difficult conditions of an acute epidemic (2,3).

2. Collection and use of Convalescent Plasma or Serum

2.1 Role of Regulatory Agencies

If therapeutic use of convalescent plasma or serum is considered credible as a candidate intervention based on the available scientific data, regulatory agencies should first consider the ethical, scientific, and logistic resource issues that need to be addressed in order to evaluate and implement this therapy in the context of the available infrastructure in the affected countries. An organized effort to establish safe use and to determine true efficacy of this therapy has to be established by a sponsoring organization or consortium and well controlled by local regulatory authorities, potentially in close cooperation with mature regulatory authorities experienced in this field and with WHO. Supporting data from preclinical studies or related indications (infections) may sometimes be available. Such an approach is needed especially in consideration of the concern that in urgent conditions when effective vaccines and antiviral drugs are unavailable convalescent plasma or serum would be used empirically without defined standards. Such uncontrolled activities could jeopardize efficacy and safety, as well as documentation and scientific evaluation. Countries that want to engage in good practice should bring together blood and/or plasma collection establishments to design and set up a program for collection of convalescent plasma or serum and to determine the feasibility for its use. Moreover, clinical trials for proof of concept should be regulated by national authorities.
2.2 General Regulatory Considerations

A regulatory approach rather than solely a medical practice approach to empirical use of convalescent plasma or serum in the treatment of an emerging viral epidemic would have advantages in promoting patient safeguards and in the collection of useful scientific information. The following issues warrant consideration by blood regulatory authorities:

- **Clinical use of convalescent plasma or serum should be regarded as investigational**

  Because the safety and efficacy of convalescent plasma or serum are unproven in the setting of a novel epidemic, collection and clinical use of this product should be managed as an experimental therapy consistent with ethical safeguards (informed consent of donors and patients, institutional approval, special labeling) and a commitment to gather and report outcome data independently of the outcome of the study in order to prevent publication bias.

- **Standards for product manufacturing should maximize safety of donors and recipients**

  Collection and preparation should be performed by trained staff operating under standard operating procedures in regulated and certified facilities that are routinely engaged in blood and plasma collection and preparation in accordance with international guidelines (4). Selection criteria for donors should include all established safeguards for prevention of transfusion transmitted diseases. (See “WHO Blood Regulators Network (BRN): Donor selection in case of pandemic situations” at [http://www.who.int/bloodproducts/brn](http://www.who.int/bloodproducts/brn).) Additionally, clinical and laboratory standards as feasible should be established for diagnosis of a recent infection in the donor strongly correlated with the epidemic agent or condition (e.g. a case definition and/or related antibody), time post resolution of illness (where feasible nucleic acid amplification technology (NAT) to demonstrate resolution of the infection), and number and frequency of standardized collections per donor. Where possible, the titer of (neutralizing) antibodies as a measure of the putative “active substance” in the donated plasma should be determined. Safety considerations for donors should also include safeguards to prevent disease transmission to donors and health care workers. Selection of donations that are negative for HBV, HCV, HIV, syphilis or other locally transmitted infections is necessary to minimize risks. Where feasible, pathogen inactivation of plasma is highly desirable. Care should be taken to minimize disruption to the collection and processing of blood and components for other patient needs.

- **Criteria for patients to be treated**

  Development of a case definition for confirmation of disease in a candidate patient might prevent delay of therapy in settings where rapid and specific diagnostic testing is impractical. Dosing guidelines should be provided and
consideration should be given for use of units from at least two different donors in
recognition of biologic variations in the immune response. Also, it may be useful
to establish priorities for clinical use (e.g. use early in the disease course
versus use reserved for advanced disease.) Passive immune therapy is
generally more effective when given earlier in the course of disease, and
may be accomplished with lower doses than those needed for treatment in
established disease. As it is not known whether early or later treatment of
patients would be similarly effective, an ad-hoc prioritization of patient
subpopulations could limit eventual understanding of the optimal treatment
window and how best to use a product whose availability may be limited.

• General considerations for plasma products are applicable

As with other plasma therapies, attention should be given to ABO
compatibility. ABO compatibility would not be a major concern for a purified
immunoglobulin product made from large plasma pools. Antibodies against
leukocyte antigens, as frequently developed by women during pregnancies, may elicit
severe lung disease called Transfusion Related Acute Lung Injury (TRALI) which is
a rare syndrome occurring within 6 hours after transfusion of plasma. As
feasible, preference for male sourced plasma or serum (and/or testing of
female donors for antibodies to HLA and anti-granulocyte antibodies) may
minimize risk of TRALI.

• Outcome monitoring should be oriented towards determination of product
safety and efficacy and the rapid communication of best practices

Patient outcome monitoring and reporting should include indicators of safety
and efficacy. Electronically available, fillable Case Report Forms would
facilitate capture of essential data. Additionally, specimen collection from both
donors and recipients (pre- and post-treatment) should be performed to permit
retrospective determination of the characteristics of an effective product and
dosage regimen and patient collectives having most benefit. Mechanisms for rapid
aggregation of clinical experience and dissemination of information to clinicians
should be established in advance of an emerging viral epidemic.

• Potential use of small scale immunoglobulin concentrates

Administration of whole units of plasma or serum from individual collections is
limited by volume of safe administration and may preclude delivery of an
effective dose of relevant antibodies. Technology exists to prepare virally
inactivated immunoglobulin concentrates from small pools of plasma units (5).
While adding elements of cost and complexity, use of small scale concentrates
might significantly increase the dose of virus specific antibodies that can be
delivered to patients, potentially increasing their effectiveness.

• Feasibility of large scale production including manufacture of purified
immunoglobulins

The large scale production of convalescent plasma or serum may be impractical
in the early stages of an epidemic for lack of sufficient donations. If the
epidemic should widen significantly, consideration could be given to industrial scale production of a disease specific plasma derived immunoglobulin based on the outcome of studies on the effectiveness of convalescent serum or plasma. Any such product should be made only under GMP in a well-established and legally regulated facility. In settings of a recurrent epidemic, consideration could be given to identification through serosurveys of candidate donors without recent illness who have had previous exposure to the epidemic virus. Such donors could be recruited on a large scale to provide the starting materials for manufacture of a plasma derived immunoglobulin with specificity for the epidemic agent.

3. Summary

Convalescent plasma or serum should be considered as a candidate intervention in the setting of an expanding viral epidemic of public health concern for which vaccines and antiviral drugs are unavailable. Consequently, development of the infrastructure to permit safe collection and use of convalescent plasma or serum should be part of national epidemic preparedness. In a given outbreak, scientific studies on the feasibility and medical effectiveness for collection and use of convalescent plasma or serum should be explored through clinical trials that can be established concurrent with their empirical use. Acting within their mandates, regulatory agencies can play an essential role to enable progress in this area. Countries that want to engage in this type of practice should take all necessary steps to establish appropriate regulatory conditions for the collection of convalescent plasma or serum, the ethical conduct of clinical studies, and the monitoring and reporting of assessable patient outcomes. Programs conducted at the national level should ensure the use only of convalescent plasma or serum collections that meet the safety and quality criteria consistent with established regulatory standards. Small scale concentrates of immunoglobulins prepared from a limited number of convalescent plasma collections may provide products of higher potency and greater consistency than individual units. The feasibility of production on a large scale of disease specific immunoglobulin concentrates can be considered for the longer term, based on the course of the epidemic, access to large numbers of suitable plasma collections, and the available infrastructure for manufacturing such products under GMP.
4. References


