WHO Blood Regulators Network (BRN)

Position Paper on Collection and Use of Convalescent Plasma or Serum as an Element in Middle East Respiratory Syndrome Coronavirus Response*

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1. **Consideration of the use of convalescent plasma as an element in Middle East Respiratory Syndrome Coronavirus response**

1.1 **Overview**

Addressing the threat of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) has become an urgent global public health priority.

There is a high likelihood in an outbreak that large populations of susceptible persons will become ill especially early in the event, either prior to availability of vaccines and effective antiviral therapy, or if these therapies prove to be ineffective. Therefore, it is prudent to explore other options to be included in response preparedness including the production and use of convalescent plasma or serum as a useful addition to other planning measures. Based on animal models of SARS-CoV (1), the possibility exists that passive immunotherapy with convalescent plasma or serum might be effective as a therapy to reduce clinical consequences of infection. These reports raise the question whether strategies for collection and therapeutic use of convalescent plasma or serum should play a role in preparedness for MERS-CoV. However, the use of passive immunotherapy in MERS-CoV should also include consideration of possible adverse effects specific to a limited number of viruses including coronaviruses, with respect to immunopotentiation of infection by vaccines or by passive immunization. As an example, experimental and anecdotal evidence suggests that pre-existing antibodies to SARS-CoV may have mediated enhanced disease (2). MERS-CoV infection is associated with renal impairment and replication in the kidney (3). Consequently, the safety and effectiveness of convalescent plasma or serum for treatment of MERS-CoV infections remains to be explored. Development of fractionated immunoglobulins or monoclonal antibodies also might be considered.

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 general use fell into disfavour after the advent of antibiotic therapies and in
consideration of the problems of adverse reactions to animal derived sera and whole serum. However, human and animal derived immunoglobulins remain important therapies for a variety of conditions (parvovirus, CMV, hepatitis B, rabies, hepatitis A, botulism, envenoming, etc.) Additionally, there is precedent in the modern era for effective management of Argentine Hemorrhagic Fever (Junin Virus) with immune plasma as part of a nationally organized response (4). By analogy, although there are many uncertainties, the possibility exists that convalescent plasma might play a role in the urgent response to MERS-CoV in settings where vaccination and/or effective antiviral chemotherapy is lacking.

2. Collection and use of Convalescent Plasma or Serum

2.1 Role of Regulatory Agencies

Although convalescent plasma or serum could be prepared and used locally as a medical practice, an organized effort to establish safe use and to determine true efficacy of this therapy has to be established by applicants and well controlled by regulatory authorities. Such an approach is needed especially in consideration of the likelihood that convalescent plasma or serum will be used empirically without defined standards in urgent conditions when effective vaccine, antiviral drugs and antimicrobial agents are unavailable or prove to be inadequate. In conjunction with public health agencies, regulatory authorities could play a role in identifying the need for a scientific evaluation in this area. Countries which want to engage in this type of practice should bring together blood and/or plasma collection establishments to design and set up a programme for collection of convalescent plasma or serum and to determine the feasibility for its use. Moreover, design of clinical trials for proof of concept should be regulated by national authorities. For example, it is suggested that efforts could be directed to carrying out trials using convalescent plasma, serum or immunoglobulin prepared from individuals who have convalesced from MERS-CoV.

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 MERS-CoV 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, clinical use of this product should be managed as an experimental therapy consistent with ethical safeguards (informed consent, institutional approval,
special labelling) and a commitment to gather and report outcome data independently of the outcome of the study (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 (5). 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, standards should be established for diagnosis of recent severe acute respiratory infections in the donor (e.g. a case definition and/or antibody titer), time post resolution of illness, and number of standardized collections per donor. Safety considerations for donors should also include safeguards to prevent MERS-CoV transmission. Where feasible, pathogen inactivation of plasma is 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 specific diagnostic testing is impractical. Also, it may be useful to establish priorities for clinical use (e.g. use early in onset of MERS-CoV vs. use reserved for advanced disease such as pneumonia). Conversely, since it is not known whether early or later treatment would be effective, prioritization could limit understanding of the treatment window. 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.

- **General considerations for plasma products are applicable**

As with other plasma therapies, attention should be given to ABO compatibility. 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 TRALI1. 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. ABO compatibility would not be an issue for an immunoglobulin product.

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1 Transfusion related acute lung injury (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. Mechanisms for rapid aggregation of clinical experience and dissemination of information to clinicians should be established in advance of a pandemic.

• **Feasibility of large scale production including manufacture of immunoglobulins**

At the present time, the epidemic of MERS-CoV has remained small with several hundred documented cases and predominant localization in several countries of the Middle East ([http://www.who.int/csr/disease/coronavirus_infections/en](http://www.who.int/csr/disease/coronavirus_infections/en)). Consequently, the large scale production of convalescent serum or plasma is impractical. Similarly, the limited extent of the epidemic calls into question the feasibility for large scale production of an anti-MERS-CoV immunoglobulin. In the event that the epidemic should widen significantly, consideration could be given to industrial scale production of a specific human 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.

3. **Summary**

The WHO Blood Regulators Network recommends that scientific studies on the feasibility and medical effectiveness for collection and use of convalescent plasma or serum be explored through clinical trials. In particular, an opportunity exists to study the feasibility, safety and effectiveness of convalescent plasma or serum and possibly other passive immunotherapies in MERS-CoV. Acting within their mandates, regulatory agencies can play an essential role to enable progress in this area. Countries which 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 conduct of clinical studies and the monitoring and reporting of patient outcomes. Programmes conducted at the national level should ensure the use only of convalescent plasma or serum collections that meet the safety, quality and efficacy criteria consistent with established regulatory standards. The feasibility of production on a large scale, possibly including a specific immunoglobulin, should be considered based on the outcome of studies, the course of the epidemic, and the available infrastructure for manufacturing under GMP.
4. References


