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Guidelines

Use of Convalescent Plasma in COVID-19 Patients

Objective

To provide public health facilities, health care settings, health care professionals and public, the general guidelines regarding use of “Convalescent Plasma” as Experimental therapy for COVID-19 patients in Pakistan.

Rationale

COVID-19 is currently responsible for pandemic and is a threat to global health. No specific, effective therapy/drugs are available for its treatment, supported by strong evidence, so far. Convalescent plasma (CP) therapy, a passive immunotherapy, that has been applied to the prevention and treatment of many infectious diseases for more than a century including SARS, MERS, and 2009 H1N1 pandemic shows promise, with some encouraging efficacy and safety reports^{1,5}

The experiences, mainly from China on the feasibility and efficacy of convalescent plasma (CP) transfusion in COVID 19 patients^{1,5}, have been published, however the randomized trials are still awaited.¹FDA has included CP into the list of Investigational New Drugs (INDs) due to exceptional and emergent situation arising from pandemic of COVID-19⁶. The nation-wide trial in USA led by Mayo Clinic under uniform protocol has made preliminary safety data on usage of CP but not the efficacy results. First systematic review by Cochrane Collaboration is also publicly available. Pakistan has also been affected with this pandemic and some experts in country are suggesting the use of CP as an experimental treatment. However, the results of ongoing trials are being constantly evaluated and as soon as level 1 evidence becomes available the National Guidelines for Management of COVID-19 will be updated.

With this background these general guidelines are formulated so that systematic, structured and scientific approach can be adopted by the scientific community as well as ensure best standard of care, uniformity of documentation so that results can be pooled together, and a meaningful inference can be drawn. This shall help the government to ensure safety of patients and share the local experience and inform public.

1. Facilities eligible for carrying out CP treatment

Since CP is still an experimental therapy it can only be safely used under controlled settings as part of research protocol. The Principal investigator of the research should obtain approval for



his/her protocol and must get the health facility approved by MoNHSR&C in which the therapy can be initiated under supervision. Only approved hospitals are allowed to enroll their COVID 19 patients in clinical trials which have been cleared by the relevant research regulatory authorities (MoNHSR&C)

2. Recipient of CP

Any COVID19 patient enrolled in a permitted “Clinical trial” can be eligible for receiving the investigational therapy i.e. CP under supervision of a qualified physician in an approved health facility. There could be various eligibility and ineligibility criteria based on the “Trial protocol”.

3. Donor of CP

Eligibility criterion of donor

Eligibility criterion of potential donors i.e. individuals who recovered from COVID-19 and are asymptomatic for at least two weeks. These criteria should not differ from that being recommended in clinical protocols and accepted by regulatory authorities. The other criterions should include compliance with the Donor guidelines by Safe Blood Program and Provincial Safe Blood Transfusion Authorities and any interim guidelines on CP by provincial or federal health authorities.

4. Plasma collection facilities

Voluntary Donors

The investigators of protocols should ensure that donors enrolled are voluntary, who have recorded evidence of Covid19 disease. Only voluntary donors are expected to answer health questions honestly. No remuneration of donor by health care setting or patient other than facilitating travel is permissible by health authorities and WHO guidelines. Accessing convalescent individuals, motivating and recruiting is sole responsibility of investigators of the trial.

Informed consent of donor

Informed consent of the donor should be obtained in, one to one interview with provision of full privacy and confidentiality for donor. The information in this regard should be written and structured and similar to what has been recommended by WHO. The interviewer should be qualified for this activity.

Donor hemovigilance

The donor hemovigilance form should be filled for each donor as recommended by Safe Blood Program authorities and available from www.sbtp.gov.pk. It has all essential guidelines available as technical documents.



Donor testing for transfusion transmitted infection

The blood bank responsible shall ensure that the minimum donor testing for HBV, HCV, HIV and syphilis. The technology used should be both CLIA (Chemiluminescence Assay) followed by NAAT (Nucleic acid amplification testing). To avoid wastage of expensive apheresis kit, the blood bank may opt to screen the donor prior to apheresis. The evidence of carrying out this testing should be made available for scrutiny by health authorities.

Neutralizing antibody testing and anti IgG testing

Titration of neutralizing antibody in CP donors is repeatedly referred to in literature, but it may not be possible to carry out in every hospital lab as it is very cumbersome technique, expensive and requires BSL 3 facilities at least. With availability of better testing, it is recommended that FDA and/or CE marked ELISA with more than 95% sensitivity and 98% specificity should be used for detection of total antibody and demonstrate at least titer of 160. Neutralization Titer of 80 is acceptable limit (where facility is available). It is desirable that aliquot of donor sample is saved and frozen for later testing for neutralizing antibody, when it can be arranged or outsourced.

Harvesting plasma

After meeting above prerequisites, the plasma can be harvested for the plasma volumes that is recommended, is 400 to 600 ml, depending on calculated blood volumes, tolerance of donor, experience of center and those currently used in other protocols. This collection can be aliquoted into 2 to 3 aliquots maintaining sterility and frozen.

Newer protocols of Convalescent Plasma may opt to harvest 170 ml to 200 ml from collection of one whole blood donation, will be acceptable if donor agrees, after full information and disclosure. This will however make donor ineligible for repeat donation for at least 3 months.

Aliquoting, splitting, labelling and storage of plasma

Plasma should be stored according to the duration that is expected between harvesting and its usage. It is acceptable to keep it at 4°C in blood bank and labelled as PF24, instead of FFP which is frozen within 8 hours at -30°C. If apheresis collection is done for larger volume then 2 aliquots of 400-450 ml each can be frozen, but it must be aliquoted without opening the system, using satellite bags or using sterile connection device. In current approved clinical trial, plasma is infused once only. Second dose of plasma is used in exceptional circumstances. In newer approved trials where source of plasma is whole blood, smaller volume of 170-200 ml can be infused 2-3 times as the protocol allows. It is highly recommended to explore Blood Establishment Computer Software, locally available, that is compliant with International Society of Blood Donation (ISBT)128 standards for blood bank processes and labelling. This will ensure traceability of donors to patients and vice versa without errors and ease the process of documentation.

Process of issuance and documentation

The requisition for CP plasma from blood bank and its issuance, labelling and templates used for same should be made part of clinical protocol for CP. It should be completely understood after adequate training of the staff. All measures should be taken to avoid identification errors.



Eligibility Criteria of Plasma Infusion

When the Covid-19 patient is considered for plasma infusion, following parameters are to be present (for general guidance only and can be updated with evolving evidence):

- Patient's signed informed consent
- Covid-19 PCR positive status
- Respiratory rate ≥ 30 per minutes
- Oxygen saturation of $\leq 93\%$ or less
- Pulmonary infiltrate involving $>30\%$ or more lung parenchyma

The primary and secondary outcomes of the experimental CP therapy should be clearly defined in protocol for meaningful comparisons. It is highly desirable to have parallel matched controls and a procedure of randomization. Every patient's baseline clinical data and follow up data after infusion of convalescent plasma should be recorded and shared with the clinical trial site. It is a mandatory requirement.

Current evidence suggests that CP therapy has no significant clinical benefit in critically ill patient on ventilator beyond 7 days, or patients with uncontrolled cytokine release syndrome leading to multiorgan failure. It is also not indicated in milder cases where risks outweigh the benefits.

Submission of data and publication

The data and result shall be shared with relevant health authorities and publication of results should meet the international standards. Safety data of every clinical trial pertaining to convalescent plasma should be shared with National Drug Safety Monitoring Board (DSMB) periodically. Premature release of data is not encouraged and should be avoided at all costs. A mechanism for peer review should be identified in the clinical proposal to address data quality issue.

5. Possible Side Effect

Plasma transfusions are generally safe and well-tolerated by most patients, but serious side effects have been reported. Possible side effects include but not limited to:

- febrile reactions
- allergic reactions
- transfusion associated circulatory overload
- bronchospasm
- transfusion related acute lung injury
- anaphylactic reaction in IgA deficient hosts
- transmission of diseases like HIV, hepatitis B or hepatitis C virus or others)⁴



6. Information for Public

- i. Convalescent Plasma (CP) use is one of the interventions currently under investigation in Pakistan. However, at the moment, there are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma as a standard therapy.
- ii. Realizing the dire need of effective treatment regimens for COVID-19, the Government of Pakistan has mandated DRAP to oversee testing new technologies and interventions. Clinical trials are currently underway to test the use of convalescent plasma as an investigational treatment in COVID-19 patients. Hospitals and physicians taking part in the trials can enroll their COVID-19 patients who fulfill the eligibility criteria for entering into the study.
- iii. Individuals who have fully recovered from COVID-19, are asymptomatic for at least two weeks and are willing to donate plasma can contact helpline 1166 for guidance for nearby accredited plasma donation centers and hospitals offering CP to patients under approved protocols.
- iv. The public is advised to contact the treating physician/hospital for information regarding the trial in progress and not to be exploited by paying money in purchasing Plasma from different blood banks/hospitals.
- v. Public and Physicians are advised to keep themselves informed about the clinical guidance on judicious use of convalescent plasma for COVID-19 patients in current pandemic that will be issued by the Ministry of Health from time to time.

Note: The above recommendations are being regularly reviewed by the Ministry of National Health Services, Regulations & Coordination and will be updated based on the international recommendations and best practices.

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Reference

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For more information, please contact:

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<http://covid.gov.pk/>

<http://nhsrc.gov.pk/>

<https://www.facebook.com/NHSRCOfficial>

<http://www.hsa.edu.pk/>

<https://twitter.com/nhsrcofficial>

<https://www.nih.org.pk/>

https://www.youtube.com/channel/UCdYuzeSP4Ug1f_ZZ