A review of Convalescent Plasma Therapy for COVID-19

Narendra Chirmule

Shilpa Jindani (LA): Clinical Advice
Ravi Khare, Atul Khandekar, Smritie Sheth (Pune): Risk Analysis
Dipyaman Ganguly, Brinda Kakkar, Aparna Mukherjee: Clinical Advice


Platelet Collection
VOLUNTEER DONOR

Convalescent Sera

- Passive antibody therapy, through transfusion of convalescent plasma, may prevent clinical infection or blunt clinical severity in individuals with recent pathogen exposure.
- Antibody therapy can also be used to treat patients who are already manifesting symptoms of varying severity.
- Passive antibody therapy is most effective when administered prophylactically or used early after the onset of symptoms

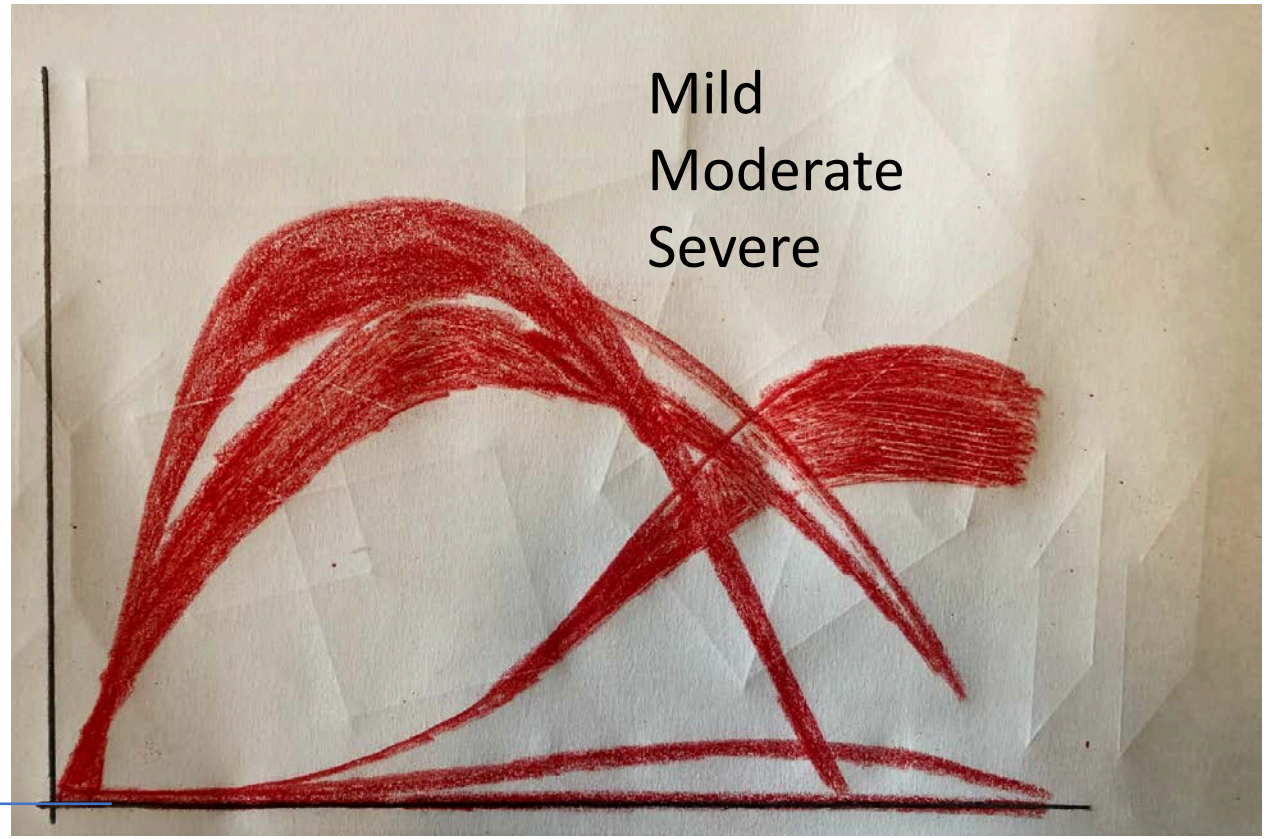
Questions

- Scientific:
  - What is the level of antibody that confers protection against infection?
  - Are ABO, Rh and other minor antigens critical to test before therapy?
- Efficacy and Safety:
  - Is convalescent plasma having impact of disease progression in patients with very severe disease already infected with the virus?
  - What safety side effects are being observed about this therapy?
- Operational:
  - When is the optimal time plasma be given to the patient?
  - How much time does the process take from identifying the patient who requires the treatment, treatment to clinical effect?

Level of “protective” antibodies to pathogens

Pathogen	Protective response	Lowest Titer reported	Protective level (95% efficacy)
Diphtheria	anti-toxin antibody	0.01 IU/ml	0.01 IU/ml
Tetanus	anti-toxin antibody	0.01 IU	0.01 IU
Pertussis	PTX*	0.8 u/ml	
HIB	PRP	125 ng/mL	>0.15 & 1.0 ugm/mL
S. Pneumonia	7-12 serotypes	0.1 ug/ml	
N. Menningitidis			2 ug
Salmonella typhii	OspA protein		1 ug
Lyme			1200 ELU/ml
Varicella	V-glycoprotein	1.25 Ab Units	5 Ab Units
Polio	Whole virus	1:2	1:8 titer
Measles	Whole virus	120 mIU	255 mIU
Mumps	Whole virus	10 Ab Units	10 Ab units
Rubella	Whole virus	10 IU/ml	10 IU/ml
HepA	Surface protein	10 mIU/ml	10 mIU/ml
HepB	Surface antigen	0.6 mIU/ml	10 mIU/mL
Rotavirus	serum neutralization	1/10 dilution	TBD
Rotavirus	serum IgA	0.0576 u/ml	TBD
HPV-6	L1	8 mMU/ml	TBD
HPV-11	L1	13 mMU/ml	TBD
HPV-16	L1	<6 mMU/ml	TBD
HPV-18	L1	13 mMU/ml	TBD

Wide range of symptoms:
asymptomatic to fatal

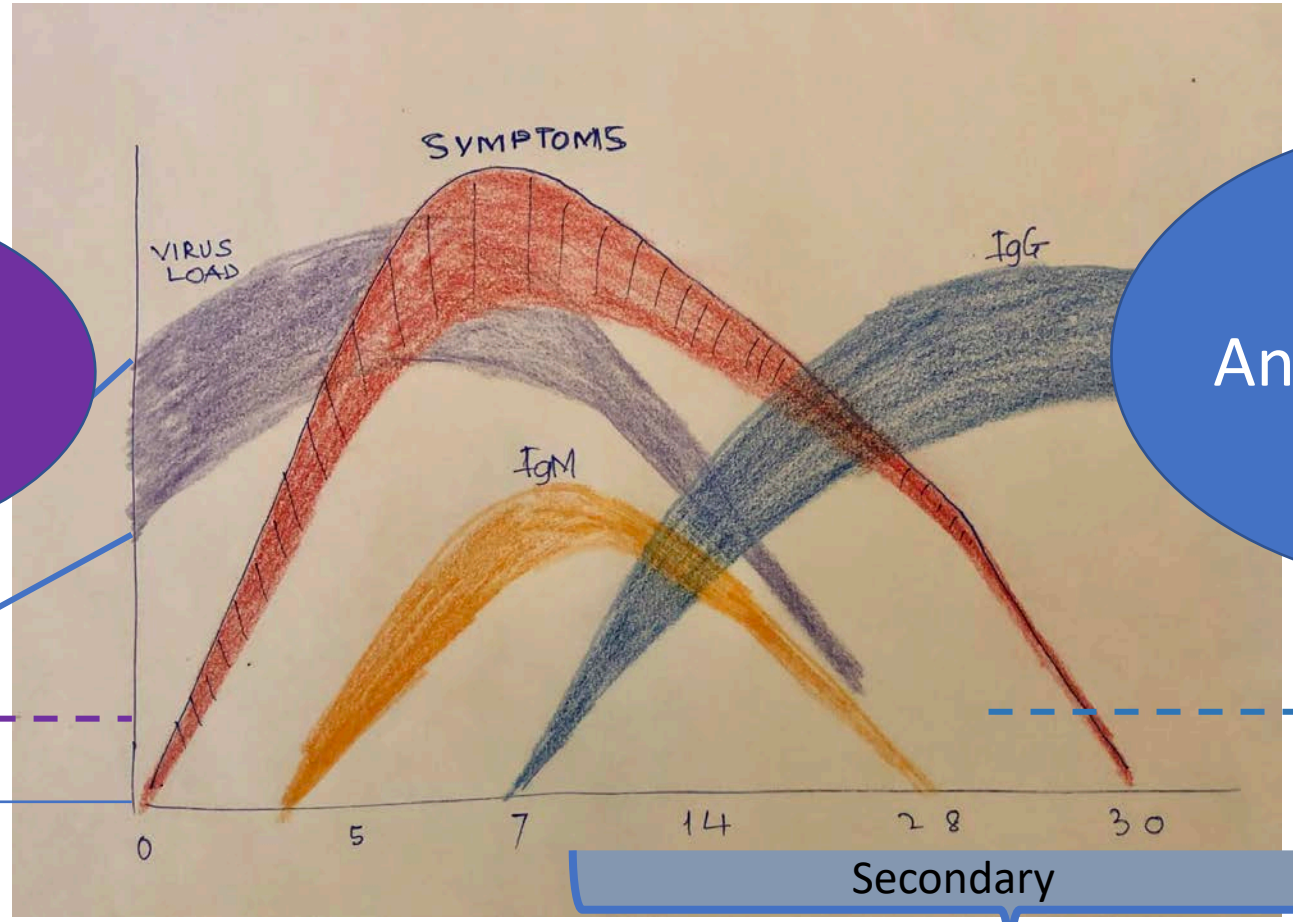


Fatal

Asymptomatic

Acute infections

Course of infection and immunity



Virus Diagnosis (carriers)

Antibody Diagnosis (exposed)

Sensitivity

Sensitivity (Protective level)

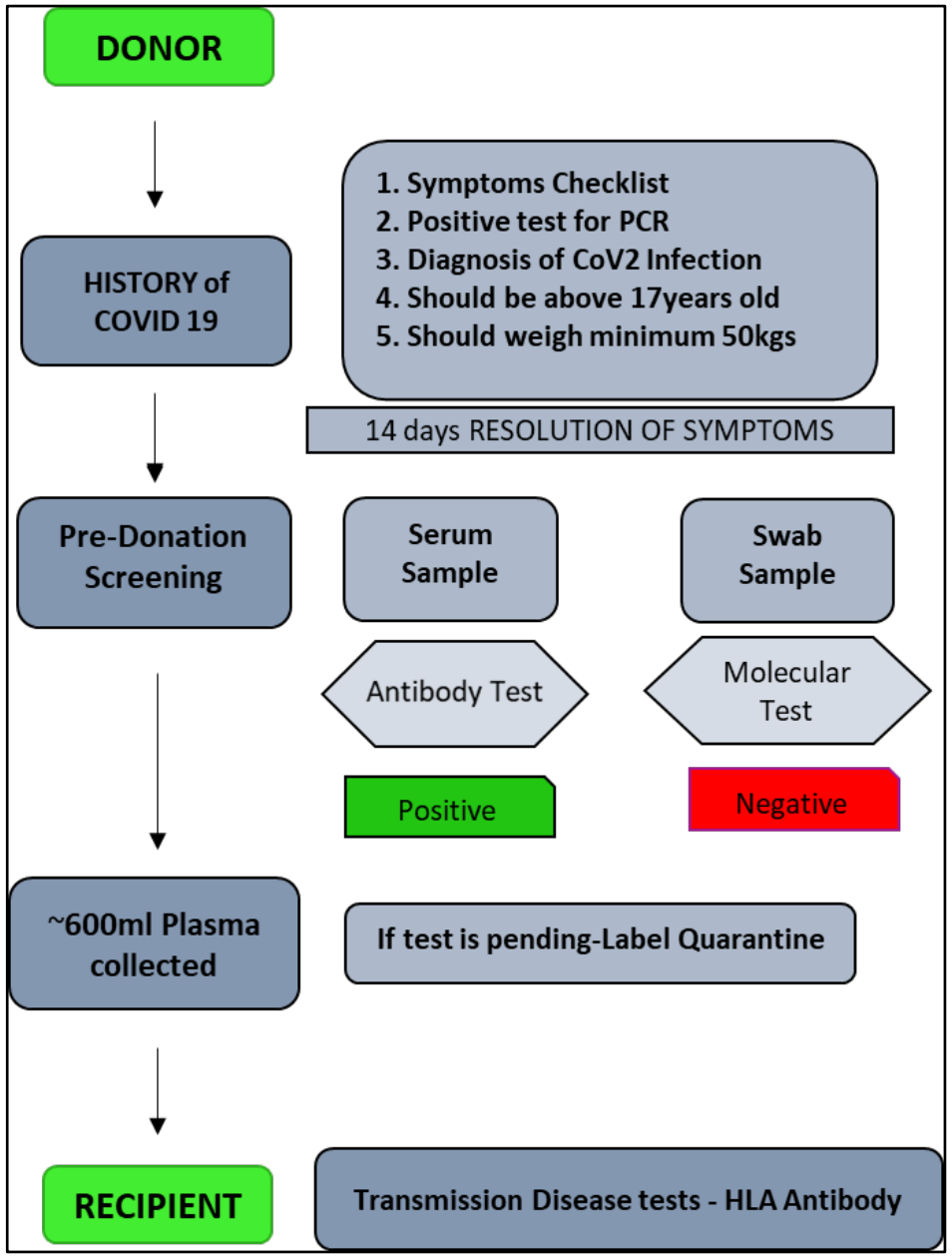
Secondary

Acute infections

Primary

Workflow

- Donor:
  - History of COVID-19 symptoms and recovery
  - Testing
  - Laboratory parameters
  - Pre-donation testing
- Recipient:
  - Criteria
  - Informed Consent
  - Risks
  - Dose?
  - Clinical Condition
  - Testing



First Covid-19 patient to undergo plasma therapy in Maharashtra dies in Mumbai

- Mumbai: A 53-year-old male patient, the first to undergo plasma therapy in Maharashtra, passed away on April 29, said Dr Ravishankar, CEO Lilavati Hospital, Mumbai.
- Plasma therapy is being used in the state on an experimental basis after getting approval from Indian Council of Medical Research (ICMR).
- **RISK:** Cautioning about the risks of using plasma therapy, ICMR had noted that convalescent plasma therapy comes with its own share of technical challenges, like antibody titer testing. There are also several risks of using this therapy including life-threatening allergic reactions and lung injury.

https://www.livemint.com/news/india/first-coronavirus-patient-to-undergo-plasma-therapy-in-maharashtra-dies-in-mumbai-11588304953927.html

Dosing

- 5 mL/kg of plasma at a titer of 1:160
- Considering first-order linear proportionality, 3.125 mL/kg of plasma with a titer of >1:64 would provide an equivalent immunoglobulin level to one-quarter of 5ml/kg plasma with a titer of 1:160.
-
- For a typical patient (~80 Kg), this would result in 250 mL of plasma (3.125 ml/kg x 80 kg = 250 mL > 1:64), approximating the volume of a standard unit of plasma in the US. This scheme imparts logistical ease to product

Who (Ebola protocol

Phase II Convalescent Plasma Study: Update

- "A Phase II, Open Label, Randomized Controlled Study to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID19 Associated Complications"

- on April 12th, 2020. The response has been overwhelming and we have received 99 applications.

At this moment ICMR does not recommend this as a treatment option outside of clinical trials.

Requirements for the trial

Each Institute that wishes to participate in the study will need to mandatorily obtain ethics clearance locally through their Institutional Ethics Committee.

1. Prior experience in conducting clinical studies.
2. Presence of necessary expertise, equipment and infrastructure for the study.
3. Ability to support the cost of care of study participants.
4. Institutional Ethics Committee registered with the CDSCO.
5. Each participating institute will have to buy trial insurance and ICMR will reimburse the premium costs as per rules.
6. Eligible institutes will be funded by ICMR for study related activities after completion of requisite documentation.

Regulatory (Guidance Document)

- On 24 March 2020, the United States (US) Federal Drug Administration (FDA) published its guidance for Investigational COVID-19 Convalescent Plasma.
    1. Emergency use investigation new drug (IND) application. This guidance does not allow for prophylaxis.
    2. Traditional pathway to apply for an IND to support research (e.g. for clinical trials).
    3. Government-led initiative to provide expanded access of convalescent plasma to participating institutions under a master treatment protocol.

https://www.fda.gov/media/136798/download

https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma

Clinical Improvement in Patients With Severe and Life-threatening COVID-19A Randomized Clinical Trial

- **Objective** To evaluate the efficacy and adverse effects of convalescent plasma therapy for patients with COVID-19.
- **Design, Setting, and Participants** Open-label, multicenter, randomized clinical trial performed in 7 medical centers in Wuhan, China, from February 14, 2020, to April 1, 2020, with final follow-up April 28, 2020. The trial included 103 participants with laboratory-confirmed COVID-19 that was severe (respiratory distress and/or hypoxemia) or life-threatening (shock, organ failure, or requiring mechanical ventilation). The trial was terminated early after 103 of a planned 200 patients were enrolled.
- **Intervention** Convalescent plasma in addition to standard treatment (n = 52) vs standard treatment alone (control) (n = 51), stratified by disease severity.
- **Main Outcomes and Measures** Primary outcome was time to clinical improvement within 28 days, defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale (ranging from 1 [discharge] to 6 [death]). Secondary outcomes included 28-day mortality, time to discharge, and the rate of viral polymerase chain reaction (PCR) results turned from positive at baseline to negative at up to 72 hours.
- **Results** Of 103 patients who were randomized (median age, 70 years; 60 [58.3%] male), 101 (98.1%) completed the trial. Clinical improvement occurred within 28 days in 51.9% (27/52) of the convalescent plasma group vs 43.1% (22/51) in the control group (difference, 8.8% [95% CI, −10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; *P* = .26). Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the convalescent plasma group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; *P* = .03); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the convalescent plasma group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; *P* = .83) (*P* for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; *P* = .30) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; *P* = .12). Convalescent plasma treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; *P* < .001). Two patients in the convalescent plasma group experienced adverse events within hours after transfusion that improved with supportive care.
- **Conclusion and Relevance** Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment, compared with standard treatment alone, did not result in a statistically significant improvement in time to clinical improvement within 28 days. Interpretation is limited by early termination of the trial, which may have been underpowered to detect a clinically important difference

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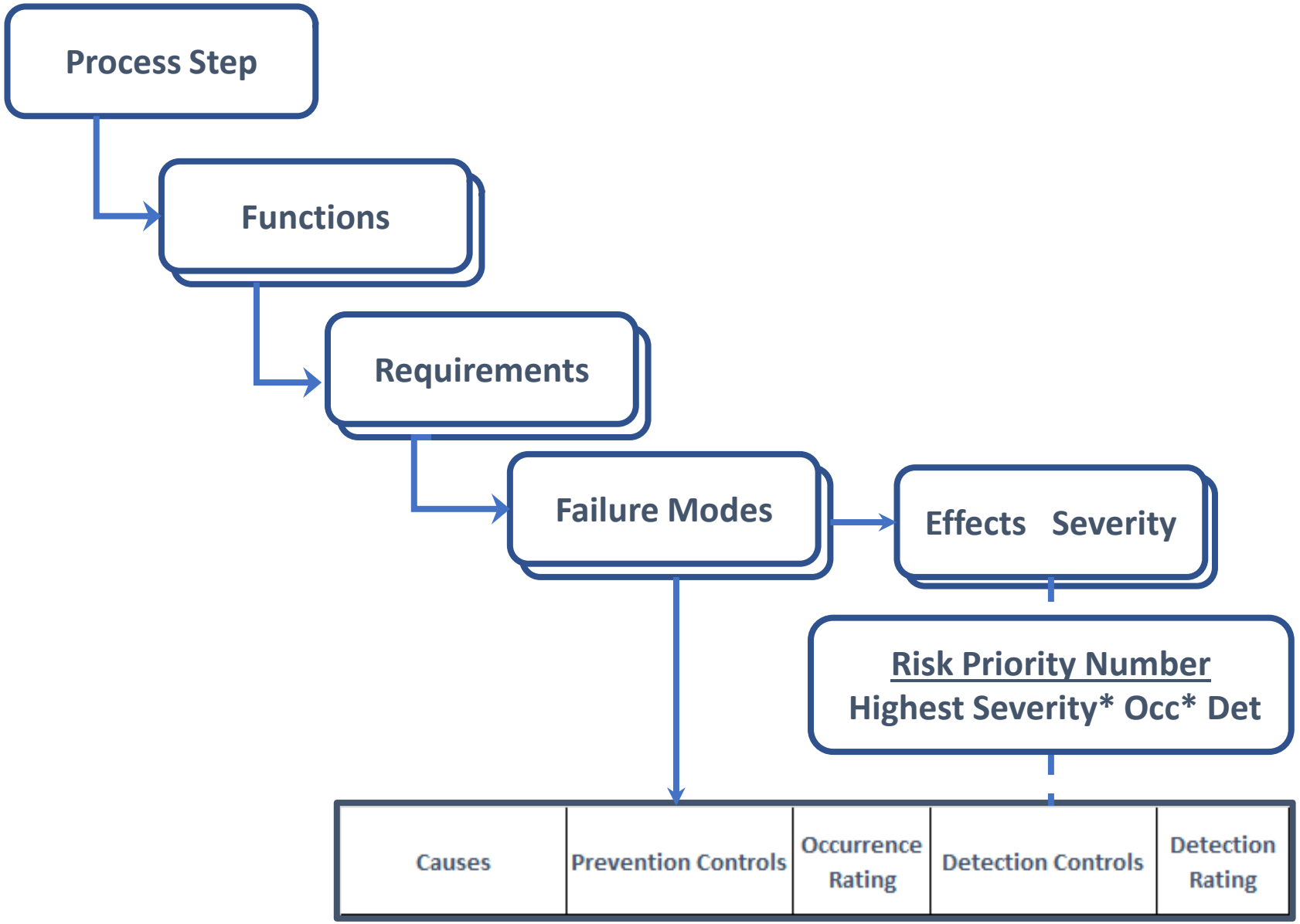
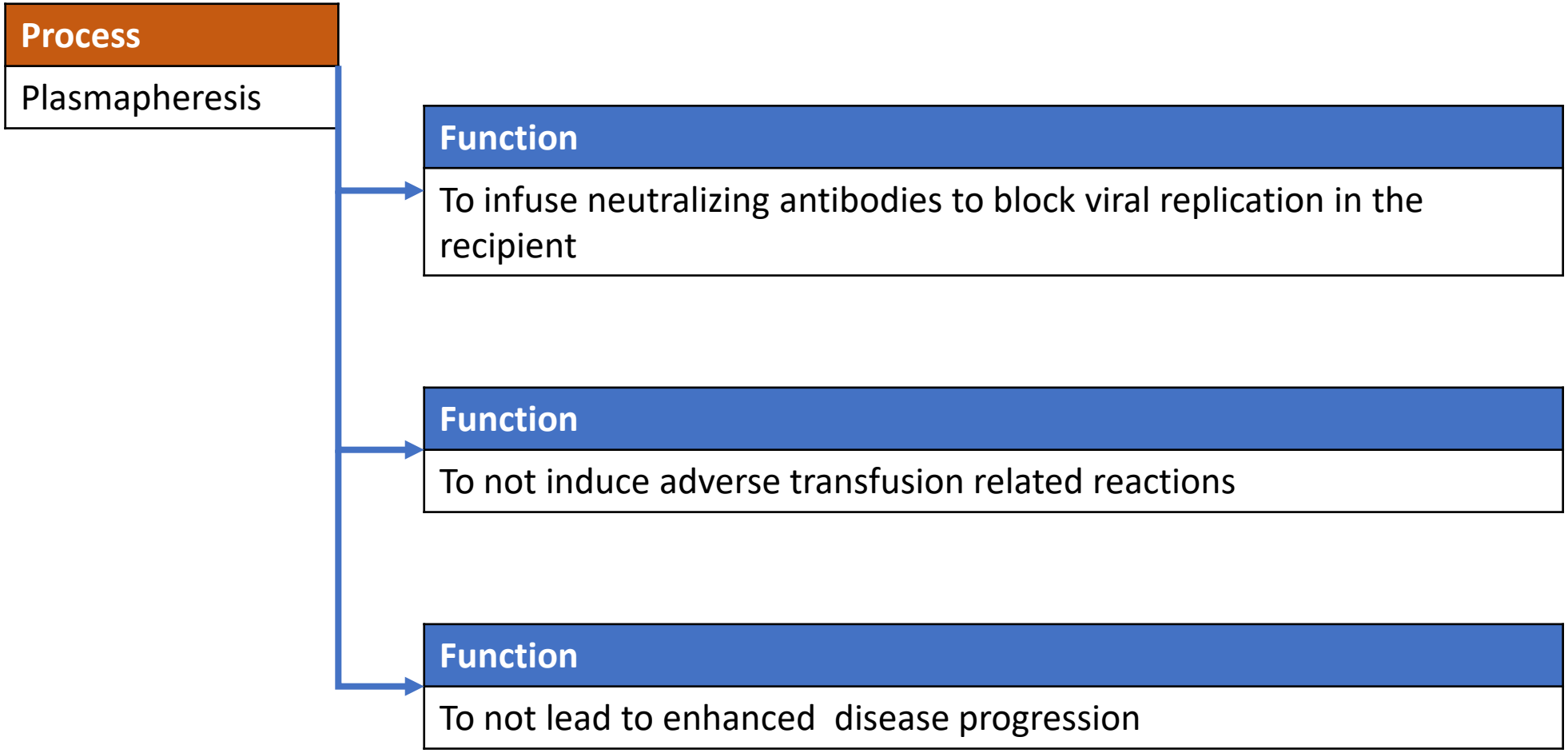
Risks

- Risk of transfusion-transmissible infection is very low. Typically cited estimates are less than one infection per two million donations for HIV, hepatitis B and hepatitis C viruses
- Allergic transfusion reactions, transfusion associated circulatory overload (TACO), and transfusion related acute injury (TRALI).
- Risks pertaining to Human Anti-SARS-CoV-2 plasma include transfusion-transmitted SARS-CoV-2 (Low)
- There is also the theoretical possibility of antibody-dependent enhancement (ADE) following transfusion.


Process Step
Functions
Requirements
Failure Modes
Effects Severity
Risk Priority Number
Highest Severity* Occ* Det
Causes
Prevention Controls
Occurrence Rating
Detection Controls
Detection Rating

What is the purpose of plasma therapy?
क्या होना चाहिए ?



What should plasma therapy do?

कितने हद तक होना चाहिए ?

Function

To infuse neutralizing antibodies to block viral replication in the recipient

Requirement

Neutralizing antibodies transfused should be adequate to clear SARS CoV2 virus completely in a COVID-19 Patient

RPN

- Risk Priority Number = Severity x Occurrence x Detection

Failure Mode

Antibodies not adequate to completely clear the Virus

Effect	Sev
This failure will lead to the progression of the disease	9

Cause Description	Prevention Controls	Occ	Detection Controls	Det	RPN
Lower Level of neutralising antibodies are infused which are not sufficient for clearance of the Virus	The current method to prevent infusion of lower levels of neutralising antibodies in the patient, is to infuse atleast 1:160 Titre of the donor plasma	4	The detection of efficacy of infusion is currently done by quantitating viral load before and after treatment	2	72
Neutralising antibodies do not reach the lungs due to compromised circulatory system (Cancer, cardiovascular disease, Diabetes)	None	5	Patient History	3	135

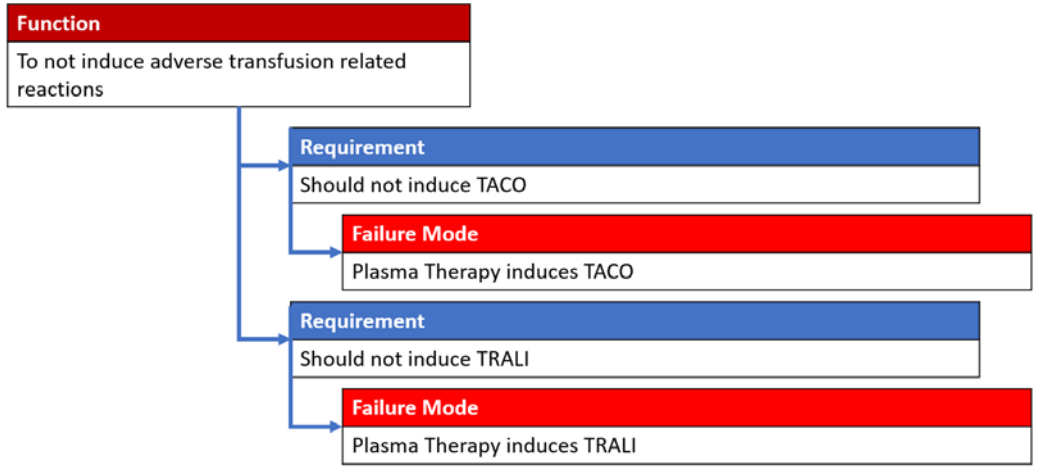
What is the effect of the FM?

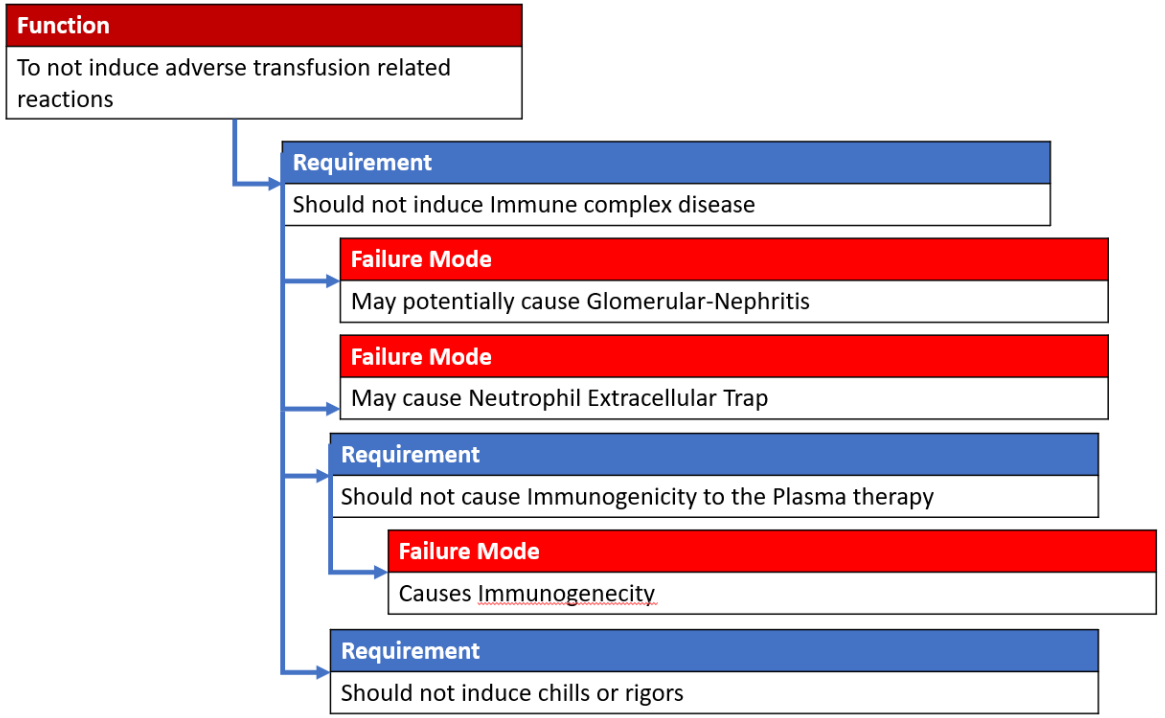
इसका असर क्या होगा ?

How did it happen?

यह क्यूं हुआ ?

FMEA performed on several functions and potential failures





Risk	Effects with highest Severity	Severity Ranking	Prevention (Action)	Treatment (Action)	RPN	Ref
Anaphylactic	Death with warning	10		Antihistamines; Epinephrine, hemodynamic stabilization and airway management	490	[14]
Cytokine Storm	Death	10		Tocilizumab treatment	210	[18]
TRALI	Death	8	Ensuring the Quality of the plasma sample prior to the plasma therapy	Discontinue Transfusion, contact blood bank Supportive Management: Maintain sufficient Ventilation/Oxygen Supply Control hemodynamic parameters Anti-inflammatory therapy with IV steroids (only in specific circumstances	32	[16]
NET-Induced Lung Inflammation	Death	8			320	[17]
Immune Complex mediated Glomerular Nephritis	Death with warning	7		Corticosteroids treatment	63	[15]
TACO	Death	7		Discontinue Transfusion Fluid mobilization with diuretics. Supplementary oxygen, and Assisted ventilation if indicated. NIPPV if ineffective, intubation may be required	98	[16]
Transmission of Infections	Death			Screening of donor samples		

Risk	Effects with highest Severity	Treatment (Action)
Anaphylactic	Death with warning	Antihistamines; Epinephrine, hemodynamic stabilization and airway management
Cytokine Storm	Death	Tocilizumab treatment
TRALI	Death	Discontinue Transfusion, contact blood bank
		Supportive Management:
		Maintain sufficient Ventilation/Oxygen Supply
		Control hemodynamic parameters
		Anti-inflammatory therapy with IV steroids (only in specific circumstances
NET-Induced Lung Inflammation	Death	
Immune Complex mediated Glomerular Nephritis	Death with warning	Corticosteroids treatment
TACO	Death	Discontinue Transfusion
		Fluid mobilization with diuretics.
		Supplementary oxygen, and
		Assisted ventilation if indicated. NIPPV if ineffective, intubation may be required
Transmission of Infections	Death	Screening of donor samples

References

- file:///C:/Users/chirm/Downloads/Convalescent%20Plasma%20Protocol%20WorkFlow%20-%202020.pdf
- file:///C:/Users/chirm/Downloads/jama_shen_2020_pc_200002.pdf
- https://www.utmb.edu/bloodbank/blood-bank-transfusion-services/component-therapy/plasma

- Additional Information

Level of “protective” antibodies to pathogens

Pathogen	Protective response	Lowest Titer reported per Assay	Protective level (95% efficacy)	Fold Rise	% Expected Response Rate	Ref
Diphtheria	anti-toxin antibody	0.01 IU/ml	0.01 IU/ml	4fold rise	95-85%	
Tetanus	anti-toxin antibody	0.01 IU	0.01 IU	4fold rise	95-85%	7
Pertussis	PTX*	0.8 u/ml		4fold rise	85-70%	
HIB	Polyribosylribitol phosphate (PRP)	125 ng/mL	>0.15 & 1.0 ugm/mL			
S. Pneumonia	7-12 serotypes	0.1 ug/ml		2-4 fold rise		
N. Menningitidis			2 ug			
Salmonella typhii	OspA protein		1 ug			
Lyme			1200 ELU/ml			
Varicella		1.25 Ab Units	5 Ab Units			
Polio		1:2	1:8 titer			
Measles		120 mIU	255 mIU			
Mumps		10 Ab Units	10 Ab units			
Rubella		10 IU/ml	10 IU/ml			
HepA		10 mIU/ml	10 mIU/ml			
HepB		0.6 mIU/ml	10 mIU/mL			
Rotavirus	serum neutralization	1/10 dilution	TBD			
Rotavirus	serum IgA	0.0576 u/ml	TBD			
HPV-6		8 mMU/ml	TBD			
HPV-11		13 mMU/ml	TBD			
HPV-16		<6 mMU/ml	TBD			
HPV-18		13 mMU/ml	TBD			
Tuberculosis						
Yellow fever						
RSV						

RISK ANALYSIS