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CONVALESCENT PLASMA THERAPY FOR COVID-19: STATE OF THE ART.

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Abbreviations : ADE : antibody-dependent enhancement; CBP : convalescent blood product; COVID-19 : coronavirus disease 2019; CP : convalescent plasma; CWB : convalescent whole blood; ELISA : enzyme-linked immunosorbent assay; EVD : Ebolavirus disease; IVIG : intravenous immunoglobulins; MERS : Middle-East respiratory syndrome; PRNT : plaque reduction neutralization test SARS : severe acute respiratory syndrome; TRALI : transfusion-related acute lung injury ; TTI : transfusion-transmitted infection.

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Abstract

Convalescent blood product therapy has been introduced since early 1900s to treat emerging infectious disease based on the evidence that polyclonal neutralizing antibodies can reduce duration of viremia. Recent large outbreaks of viral diseases for whom effective antivirals or vaccines are still lacking has revamped the interest in convalescent plasma as life-saving treatments. This review summarizes historical settings of application, and surveys current technologies for collection, manufacturing, pathogen inactivation, and banking, with a focus on COVID-19.

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Introduction

Emerging viruses rarely provide time to develop vaccines, and prophylactic vaccines are rarely effective in therapeutic setting. Antivirals are currently available only for selected viral families, are often not affordable to developing countries, and their manufacturing is hard to scale up in short times.

Recent viruses with pandemic potential include flaviviruses (e.g. West Nile virus (WNV), dengue virus, Zika virus (1)), chikungunya virus (2), influenzaviruses A, e.g. A(H1N1), A(H5N1) (3), Ebola virus (EBOV) (4), and respiratory betacoronaviruses (SARS-CoV (5), MERS-CoV (6), and SARS-CoV2 (7)).

Transfusion of convalescent blood products (CBP), especially convalescent plasma (CP), are useful against emerging infectious agents if the latter induces neutralizing antibodies (8). CBPs are manufactured by sampling whole blood or apheresis plasma from a convalescent donor.

Donor selection should be based according to neutralizing antibody titer as assessed with the plaque reduction neutralization test (PRNT), which requires a viable isolate, replication-competent cell lines and skilled personnel. Since PRNT takes time to be setup and requires expensive facilities, in resource-poor settings or in time-sensitive scenarios, collection with retrospective PRNT or ELISA assays targeting recombinant receptor binding domains (RBD) of the viral antireceptor has often been implemented: under these circumstances ELISA ratios/indexes have shown very high correlation with PRNT titres (9, 10). Current understanding of neutralization suggests that the virus-blocking effect is related to the number of antibodies coating the virion, whose stoichiometry is in turn affected by antibody concentration and affinity : since ELISA doesn't say anything about antibody affinity or domain specificity, it can't clear concerns for antibody-dependent enhancement (ADE) (see paragraph below).

The donor should preferably live in the same area as the intended recipient(s) to consider mutations of the target viral antigens, even if in areas epidemic for other infectious diseases (e.g. malaria) this could represent a contraindication. Although the recipient is already infected, theoretically transmission of more infectious particles could worsen clinical conditions. For this reason, the right timing of collection is

fundamental to ensure no transmission of the pathogen to the recipient. Nevertheless, such concern can be somewhat reduced by treatment with modern pathogen inactivation (PI) techniques.

The main accepted mechanism of action for CBP therapy is clearance of viraemia, which typically happens 10–14 days after infection (11). So CBP has been typically administered after early symptoms to maximize efficacy. Concurrent treatments might synergize or antagonize CP efficacy (e.g. polyclonal intravenous immunoglobulins or steroids) (12).

In the setting of respiratory viral infections, secretory IgA, which are the main immunoglobulin isotype on mucosal surfaces, are key players. They are made of 2 IgA molecules (dimers), a joining protein (J chain), and a secretory component. IgM and IgA are actively transported across epithelia by the polymeric Ig receptor (pIgR) or by neonatal Fc receptor (FcRn), while IgG can passively trasudate into alveolar fluids (13). The lung requires specific antiviral IgG_{2a} for protection in terminal bronchioles and alveoli (14, 15).

Given the emergency related to the COVID-19 pandemic, this review summarized historical settings of application, and surveys current technologies for collection, manufacturing, pathogen inactivation, and banking, of convalescent blood products, with a specific focus on possible applications for COVID-19.

Convalescent plasma and pathogen inactivation

Convalescent whole blood (CWB), in addition to antibodies, provides control of hemorrhagic events, as in Ebolavirus disease, if transfusion occurs within 24 hours in order to keep viable platelets and clotting factors. Nevertheless, convalescent plasma (CP) best fits developed countries standards and settings where antibodies only are required. CP should be collected by apheresis in order to ensure larger volumes, more frequent donations, and do not cause unnecessary anemia in the donor. Double filtration plasmapheresis (DFPP) using fractionation filter 2A20 is under investigation as an approach to increase IgG yield by 3-4 times (see NCT04346589 in Italy in Table 1): since DFPP-derived plasma is not an ordinary blood component but rather a discard product, additional regulations could apply in different countries.

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Technologies to virally reduce plasma (pathogen inactivation)

Although neither the US Food and Drug Agency (FDA)(16) nor the European Center for Disease Control are recommending pathogen reduction technologies (PRT) for CP (17), in several settings donor screening and conventional NAT viral testing (i.e. HIV, HCV and HBV NAT) could not be enough to ensure CP safety. Under this scenario, additional virological testing and PRT approximately double the final cost of the therapeutic dose. Several technologies for PRT have been approved and are currently marketed.

Solvent/detergent (S/D)-filtered plasma provides quick > 4 logs inactivation of most enveloped viruses: although the technology was developed and is massively used for large plasma pools, small scale reduction has been reported. The technology relies over 1% tri (*n*-butyl) phosphate/1% Triton X-45, elimination of solvent and detergent via oil extraction and filtration, and finally sterile filtration (18). Filtration across 75–35 nm hollow fibers could remove large viruses while preserving IgG [48], but has not been implemented yet.

In recent years photo-inactivation in the presence of a photosensitizer has become the standard for single unit inactivation: approved technologies include combination of methylene blue + visible light (19) (Theraflex®), amotosalen (S-59) + ultraviolet A (20) (Intercept®), and riboflavin + ultraviolet B (21) (Mirasol®). These methods do not to affect immunoglobulin activity.

Fatty acids are also an option. In 2002 it was reported that caprylic acid (22) and octanoic acid (23) were as effective as S/D at inactivating enveloped viruses.

Heat-treatment of plasma has been used in the past (24, 25) but goes with the risk of aggregation of immunoglobulins (26, 27).

Pooling

Large-pool products

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Pharmaceutical-grade facilities typically pool 100/2500 donors to manufacture S/D-inactivated plasma Intravenous immunoglobulins (IVIGs) are similarly prepared from pools of 2000–4000 L of plasma (or 100-1000 L in the case of hyperimmune IVIG) (28) (29). Such size can be hardly matched from CP donors and facilities rearrangement poses hard GMP issues (29).

Mini-pool fractionation scale (MPFS) into immunoglobulins

In order to be economically sustainable contract fractionation typically requires well over 10 000 liters of plasma per year, and domestic fractionation typically over 100 000–200 000 liters per year in addition to start-up a fractionation facility. A “on the bench” MPFS process (5-10 liters of plasma, i.e. approximately 20 recovered plasma units) using disposable devices and based on caprylic acid precipitation is under development in Egypt since 2003, and has been proven effective at purifying coagulation factors (30) and immunoglobulins (6-fold enrichment) (31). The same disposable bag system has also been combined with S/D reduction (18).

Lessons from SARS

SARS-CoV RNA was found in respiratory specimens from one third of patients for up to 4 weeks following symptoms (32). SARS-specific antibodies usually persist for 2 years(33), and decline in prevalence and titers occurs in the third year (34). Convalescent anti-SARS immunoglobulins were manufactured on a small scale (8, 35). Three infected healthcare workers with SARS progression despite treatment survived after transfusion with 500 ml CP: viral load dropped to zero one day after transfusion (36). Soo *et al* reported in a retrospective nonrandomized trial that treatment with CP (titre > 1:160) in 19 patients was associated with shorter hospital stay and lower mortality than in continuing high-dose methylprednisolone (37). Amotosalen photochemical inactivation of apheresis platelet concentrates demonstrated a >6.2 log10 mean reduction of SARS-CoV (38). Theraflex˚ reduces infectivity of SARS-CoV in plasma (39). Heating at

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60°C for 15-30 minutes reduces SARS-CoV from plasma without cells (40), while 60°C for 10 hours is required for plasma products (41). In addition, SARS-CoV was found to be sensitive to S/D, (40, 42).

Lessons from MERS

Antibody responses to MERS persist for less than 1 year and magnitude correlates with the duration of viral RNA shedding in sputum (but not with viral load). Mild patients have very low titers, making CP collection challenging in MERS convalescents (43). A study reported that only 2.7% (12 out of 443) exposed cases tested positive with ELISA, and only 75% of them had reactive microneutralization assay titers (44). CP with a PRNT titre ≥1:80 provide clinical benefit in MERS (45). A case of TRALI following CP transfusion in a patient with MERS was reported (46, 47). MERS-CoV load in plasma was reduced by Theraflex® (48), Intercept® (49), Mirasol® (50), and 56°C heating for 25 minutes (51) : in all cases passaging of inactivated plasma in replication-competent cells showed no viral replication.

Convalescent plasma for COVID-19

As soon as the COVID-19 pandemic appeared (7, 52), several authors suggested CP as a potential therapeutic (53, 54). Of interest, the most critically ill patients show prolonged viremia (strongly correlated with serum IL-6 levels) (55), which leaves room for therapeutic intervention with antivirals and immunoglobulins even in late stages. Viral shedding in survivors can be as long as 37 days (52), mandating SARS-CoV2 RNA screening in CP donors. Appearance of serum IgM and IgA antibody in COVID-19 occurs since day 5 after symptom onset, while IgG is detected since day 14 (56, 57). IgG are universally detected since day 20 (58). Severe female patients generate IgG earlier and higher titers (59). Duration of anti-SARS-CoV2 antibodies in plasma remains unknown, though for other betacoronaviruses immunity typically lasts 6-12 months (60). So, a suitable donor could donate 600 ml plasma (equivalent to 3 therapeutic doses) every 14 days for a minimum of 6 months. In contrast to EVD, SARS, and MERS, most COVID-19 patients

exhibit few or no symptoms and do not require hospitalization, suggesting that the majority of convalescent donors are best sought after in the general population.

The main contraindications to CP therapy are allergy to plasma protein or sodium citrate, or selective IgA deficiency (< 70 mg/dl in patients 4 years old or greater), or having received immunoglobulins in the last 30 days. As in many other trial settings, concurrent viral or bacterial infections, thrombosis, poor compliance, short life expectancy (e.g. multiple organ failure), as well as pregnancy or breastfeeding. are also contraindications.

In a first case series from China, 5 patients under mechanical ventilation (4 of 5 with no preexisting medical conditions) received transfusion with CP with an ELISA IgG titer > 1:1000 and a neutralization titer > 40 at day 10-22 after admission. 4 patients recovered from ARDS and 3 were weaned from mechanical ventilation within 2 weeks of treatment, the remaining being stable (10).

Another Chinese pilot study (ChiCTR2000030046) on 10 critically ill patients showed that one dose of 200 mL CP with neutralizing antibody titers > 1:640 resulted in an undetectable viral load (70%), radiological and clinical improvement (9).

A third series of 6 cases with COVID19 pneumonia in Wuhan showed that a single 200 ml dose of CP (titrated by CLIA only) administered at a late stage led to viral clearance in 2 patients and radiological resolution in 5 patients (61). Pei *et al* reported successful treatment of 2 out of 3 patients with 200-500 ml doses of CP (62). Recovery from mechanical ventilation was also reported by Zhang *et al* in a single patient after CP titrated with anti-N protein ELISA (63). No improve in mortality despite viral clearance were instead reported in a retrospective observational study recruiting 6 late-stage, critically ill patients treated with gold-immunochromatography-titrated CP, when compared to 13 untreated controls (64).

Outside China, 2 cases with ARDS and mechanical ventilation were also successfully treated with 2 250-ml CP doses (titrated with ELISA only) in South Korea (65).

Table 1 lists the other ongoing CP trials in COVID-19 patients listed in World Health Organization International Clinical Trial Registry Platform (ICTRP) database. The US have developed a specific platform

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for facilitating clinical trials (https://ccpp19.org/), while the International Society for Blood Transfusion created a resource library (https://isbtweb.org/coronaoutbreak/covid-19-convalescent-plasma-document-library/) .

Typically, up to doses 200 ml each are administered at least 12 hours apart, with infusion rate 100 to 200 mL/hour.

Unfortunately, most trial in Westernized countries (on the contrary of the ones ongoing in China) seem to have no control arm, which will impair efficacy interpretation. When present, the control arm consists of best supportive care alone (typically oxygen and hydroxychloroquine 400 mg bid for 10 days) or combined with intravenous placebo or standard (nonconvalescent) plasma. Since other plasma components (e.g. aspecific immunoglobulins or isoagglutinins – see below) could contribute to clinical benefit, the latter approach is ideal for dissecting the specific contribution of neutralizing antibodies, although concerns could be raised by the thrombophilic nature of COVID-19 pathology. Even placebo control in late-stage patients refractory to former lines could pose ethical concerns because of the unresponsive nature of the disease.

Notably, several plasma manufacturers are attempting to develop SARS-CoV2-specific hyperimmune sera, (e.g. Takeda's TAK-888 merge with Biotest, BPL, LFB, Octpharma and CSL Behring joined into the "Convalescent Plasma Coalition" (66); Kedrion and Kamada joint venture (9)), while other companies are investing on genetic engineering (e.g. CSL Behring on SAB Biotherapeutics DiversitAb™ platform).

CP donor recruitment strategies

As previously proofed, donor testing for neutralizing antibodies is mandatory in upstream donor selection. Three approaches are theoretically available to recruit CP donors, everyone having pros and cons. The least cost-effective approach is screening the general periodic donor population for presence of anti-SARS-CoV2 antibodies. In endemic areas, this strategy provides many fit donors with the additional benefit of a seroprevalence study in the general population (80% of cases being asymptomatic), but requires a high budget. On the other side of the coin, recruitment of hospital discharged patients is highly cost-effective

(patients can be easily tested before discharge and tracked), but patients who have required hospitalization are highly likely to be elderlies with comorbidities, and hence unfit to donate. The intermediate approach is deploying calls to donate to positive cases under home-based quarantine: given the huge numbers, some of them are likely to be periodic donors, and home-based convalescence suggests they are fit enough to donate. Nevertheless, lessons from MERS suggest that patients with mild symptoms could have developed low-titer antibodies (44), making antibody titration even more important in the population-wide and home-based approaches.

In additional to interventional trials, in the USA at least 3 trials have been registered to create registries (e.g. NCT04359602) or collect plasma with titers > 1:64 from immune donors for banking purposes, without immediate reinfusion (e.g. NCT04360278, NCT04344977 or NCT04344015). These approaches should be ecnouraged to better face next waves of the COVID19 pandemic.

CP banking

CP is typically used as a fresh product. Aliquots can be easily achieved with modern PI kits. Banking at temperature below -25˚C (according to EDQM guidelines for ordinary plasma for clinical use (67)) is encouraged in order to translate CP in an off-the-shelf, ready-to-use product. Most regulatory system require that CP is tracked informatically as a blood component different from ordinary plasma for clinical use. The final validation label should report that the donor has tested negative at PCR for the convalescent disorder and additional microbiological tests, and describe the inactivation method. There is no evidence that a single cycle of freezing and thawing significatively affects quantity or function of immunoglobulins.

Monitoring response to treatment

CP is considered an experimental therapy, and as such phase 3 randomized controlled trials should be encouraged. Despite this recommendation, in emergency settings phase 2 trials are usually started,

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hampering efficacy analysis. Response in published trials is generally measured clinically or radiologically according to target organs. Nevertheless, surrogate endpoints can include antibody titer rise in recipient's plasma and drops in recipient's viral load. Whenever quantitative PCR is not available, cycle threshold (Ct) value increases in qualitative PCR after transfusion could be a proxy for reduced viral load.

Side benefits from CP in COVID-19

Obviously, patients with humoral immune deficiencies can benefit from polyclonal antibodies contained in CP, and patients with hemorrhagic diathesis can benefit from clotting factors.

Plasma is also likely to contain antibodies against other common betacoronaviruses associated with common cold, which have been shown to cross-react with SARS-CoV2 antigens in intravenous immunoglobulin (IVIg) preparations (68). Accordingly, IVIg lead to clinical and radiological recovery in 3 severe Chinese COVID-19 patients(69) and the same team is now leading a randomized controlled trial (NCT04261426).

After demonstration that blood group 0 healthcare workers were less likely to become infected with SARS-CoV (70), a research group proved that anti-A blood group natural isoagglutinins (which can be also found in CP plasma from blood group 0 and B donors) inhibit SARS-CoV entry into competent cells (71). Such binding could opsonize virions and induce complement-mediated neutralization (72). Since SARS-CoV2 uses the same receptor as SARS-CoV, anti-A isoagglutinins are expected to have similar effects against SARS-CoV2: accordingly, clusters of glycosylation sites exist proximal to the receptor-binding motif of the SARS-CoV (73) and SARS-CoV2 (74) S protein. A recent publication showed that the odds ratio for acquiring COVID-19 is higher in blood group A than in blood group 0 (75). COVID-19 has more severe clinical presentations and outcome in elderlies and in males: intriguingly, elderly males are known to experience reductions in isoagglutinin titers (76, 77). Studies are hence ongoing to evaluate correlations between isoagglutinin titers and outcome in blood group 0 and B patients. In the meanwhile, while preserving ABO

match compatibility, it could be wise to prefer blood group 0 and B donors for CP in COVID-19, and to titre their anti-A isoagglutinins.

Concerns

The first concern is transfusion-transmitted infection (TTI). Modern PI technologies, combined with NAT, reduces the risk for contracting additional TTIs. Most regulatory systems require additional tests (e.g. HAV RNA, HEV RNA, parvovirus B19 DNA) to be performed on CP for additional transfusion safety. CBP obtained from donors in the UK may be problematic for a couple of reasons. Currently CBP obtained from individuals who lived for at least 6 months in the UK during 1980-1996 'mad cow disease (bovine spongiform encephalopathy – BSE)' outbreak may not be acceptable in some countries (78) – or by some individuals. In addition, there is a now a recognized risk of hepatitis E the within UK blood donor population (79), most likely due to the consumption of poorly cooked pork products (80, 81), for which screening has only relatively recently been initiated (82). Although this does not preclude such SARS-CoV-2 convalescent plasma/sera being used therapeutically within the UK, these other risks should be considered during larger clinical trial or individual patient compassionate use. As per the risk of worsening the clinical picture by delivering more viral particles of the targeted virus, it is generally unlikely to worsen the underlying scenario. Respiratory betacoronaviruses produce only a mild and transient viremia. With SARS-CoV, limited replication in lymphocytes (83) leads to significant risk only for recipients of blood products with high concentrations of donor lymphocytes (peripheral blood stem cells, bone marrow, granulocyte concentrates, etc). With SARS-CoV2, viremia has been shown persists only in critically ill patients (55).

The second concern is TRALI, which can be life-threatening in patients who already are suffering from ALI. Male donors are usually preferred in order to avoid the risk of transfusing anti-HLA/HNA/HPA antibodies from parous women. In the case of COVID-19, where female patients have been shown to have higher IgG levels, this could be detrimental, and anti-HLA/HNA/HPA antibody screening could be implemented.

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Antibody-dependent enhancement (ADE) is also a theoretical concern related to passive or active antibodies (targeting S protein domains other than RBD) facilitating IgG-coated virions entry into macrophages via Fcγ receptors and/or complement receptors (84, 85), leading to activation of the RNA sensing Toll-like receptors (TLR) 3, 7 and 8, and finally to elevated production of TNF and IL-6 (so called "cytokine storm"). Genetic polymorphisms (e.g. FcγRIIa (86)) can also contribute to ADE. To date potential evidences supporting a role for ADE in COVID-19 include : 1) the correlation between disease severity and total anti-SARS-CoV2 antibody levels (87-90), including neutralizing antibodies (91, 92) ; 2) the low prevalence of symptoms in COVID-19 cases younger than 20 (who have likely not been primed by infection with the other common coronaviruses 229E or OC43, or anyway have low-affinity anti-coronavirus IgG (93)); 3) in SARS, occurrence of ADE has been shown *in vitro* at low antibody titers(94), and in patients high IgG titres and early seroconversion correlate with disease severity(95). Overall, these findings pose concerns on usage of low-titer CP units (96).

Conclusions

CP manufacturing should be considered among the first responding actions during a pandemic in the meanwhile antivirals and vaccines are tested. Despite huge competition from trials employing small chemicals, multicentre randomized controlled trials should be encouraged in order to establish efficacy and provide hints about the most effective schedule (timing and dose).

Figure 1. Summary of possible convalescent blood products (CBP). Reproduced from ref (97) under STM Permissions Guidelines as of 26 March 2020 (https://www.stm-assoc.org/intellectual-property/permissions/permissions-guidelines/).

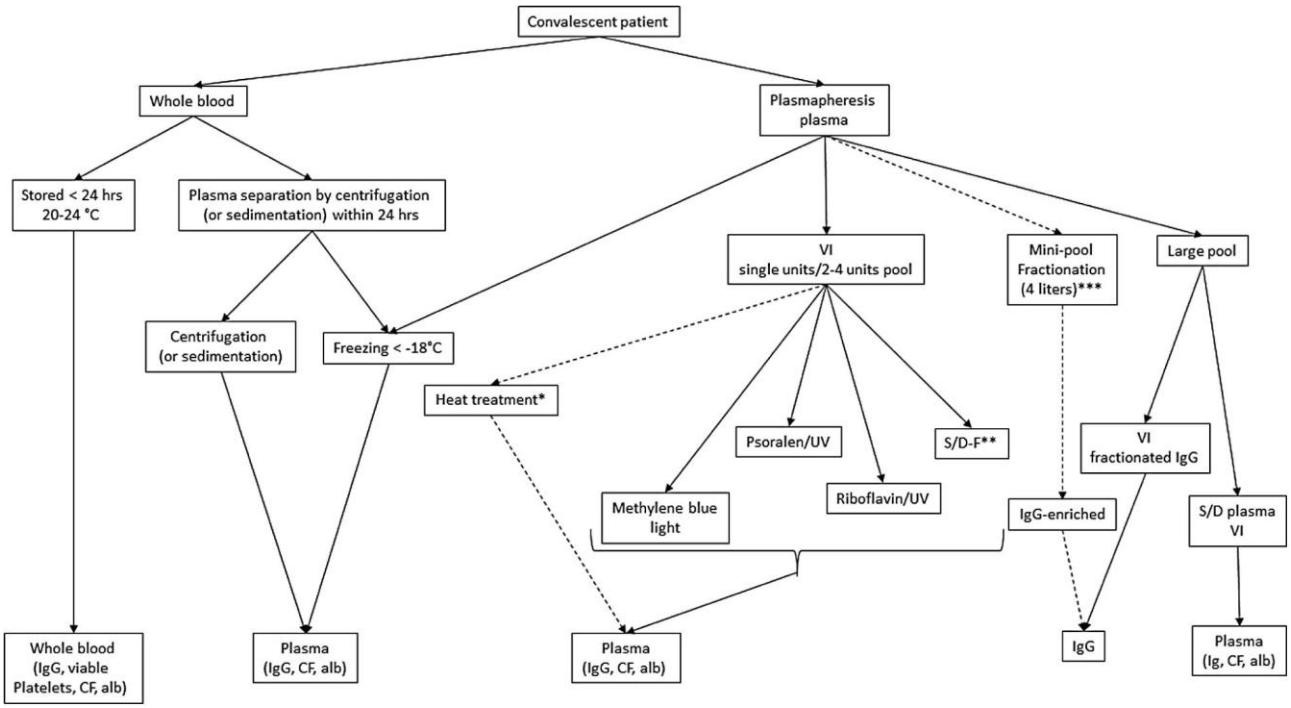

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Table 1. Ongoing interventional clinical trials of convalescent plasma in COVID-19 patients listed in World Health Organization International Clinical Trial Registry Platform (ICTRP) databases (accessed online at https://www.who.int/docs/default-source/coronaviruse/covid-19-trials.xls on April 30, 2020) and Cytel Global Coronavirus COVID-19 Clinical Trial Tracker (accessed online at www.covid-trials.org on May 9 2020). BSC: best supportive care; NA: not available; Exp: experimental group; Ctr: control group; EAP: expanded access programme.

Phase	Indication	Trial number	Country	Study population (per arm)	Schedule (vs. control arm)	Donor titer
I/II	Exposed or confirmed children	NCT04377672	USA	30	5 ml/kg = 1-2 unit (200-250 mL per unit)	>1:320
	All patients with COVID-19	NCT04292340	China	15	NA	NA
		NCT04376788	Egypt	15	exchange transfusion by venesection of 500 ml blood replacement by 1 PBRC unit + IV methylene blue 1 mg/kg IV over 30 minutes + 200 ml CP	NA
		NCT04345679	Hungary	20	1 unit of CP (200 ml)	>1:320
		NCT04356482	Mexico	90	different amounts of CP	NA
		NCT04357106	Mexico	10	1 dose of CP (200 ml)	NA
		NCT04343755	USA	55	NA	> 1:64

		NCT04360486	USA	EAP	NA	NA
		NCT04354831	USA	131	1-2 units of CP (<7 ml/kg adjusted IBW)	NA
		NCT04355897	USA	100	500 ml	NA
	Non critically ill patients	NCT04332380	Colombia	10	2 units of CP (250 ml each)/24 h	NA
		NCT04375098	Chile	30	200 ml CP on day 1 and 2	NA
		NCT04327349	Iran	30	NA	NA
		IRCT20200325046860N1	Iran	200	NA	NA
		NCT04374565	USA	29	2 units of CP (200 mL each) in 1-2 days	NA
		NCT04365439	Switzerland	10	NA	NA
	Severe or critically ill patients	NCT04321421	Italy	49	3 units of CP (250-300 mL/48h)	NA
		NCT04346589	Italy	10	DFPP-collected CP	NA
		NCT04343261	USA	15	2 units of CP	NA
		NCT04338360	USA	NA	1 unit of CP (200/250 mL)	NA
		NCT04333355	Mexico	20	1-2 units of CP (250 ml/24h)	NA
		NCT04340050	USA	10	1 unit of CP (300 ml)	NA
		NCT04347681	Saudi Arabia	40	10-15 ml CP /kg body weight	NA
		NCT04353206	USA	90	1-2 units CP on days 0 and 6	NA

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		NCT04374370	USA	EAP	1-2 units (200-400 mL per unit), not to exceed 550 mL total	NA
		NCT04358211	USA	EAP		> 160
		NCT04363034	USA	EAP up to 100		NA
		NCT04372368	USA	EAP up to 150		NA
		NCT04352751	Pakistan	2000	children < 35 kg: 15 ml/kg over 4-6 hrs; adults: < 450 - 500 ml over 4-6 hours	NA
		NCT04325672	USA	20	1-2 units of CP (300 mL/24h)	>1:64
		NCT04348877	Egypt	20	1 400 ml unit of CP	NA
III	Exposed within 96 hrs of enrollment and 120 hrs of receipt of plasma	NCT04323800	USA	150 (Exp: 75; Ctr: 75)	1 unit of CP (200/250mL) *vs*. nonconvalescent plasma	>1:64
	All patients with COVID-19	ChiCTR2000030039	China	90 (Exp: 30; Ctr: 60)	2 units of CP (200/500 mL/24h) *vs* BSC	NA
		NCT04345289	Denmark	1500 (6 arms)	1 600 ml unit of CP *vs*. sarilumab *vs* baricitinib *vs* hydroxychloroquine *vs* injective placebo *vs* oral placebo	NA
		NCT04372979	France	80 (Exp: NA; Ctr: NA)	2 units of 200-230 mL of CP *vs* nonconvalescent plasma	NA

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		NCT04374487	India	100 (Exp: NA; Ctr: NA)	up to 3 200 ml doses of CP 24 hrs apart *vs* BSC	> 1:40
		NCT04380935	Indonesia	60 (Exp: NA; Ctr: NA)	NA vs. BSC	NA
		IRCT20200310046736N1	Iran	45 (Exp: NA; Ctr: NA)	CP vs. plasma-derived immunoglobulin-enriched solution (PDIES)	NA
		NCT04342182	Netherlands	426 (Exp: NA; Ctr: NA)	1 unit of CP (250 ml) *vs* BSC	NA
		NCT04366245	Spain	72 (Exp: NA; Ctr: NA)	NA vs. BSC	NA
		NCT04344535	USA	500 (Exp: NA; Ctr: NA)	450-550 mL CP *vs* BSC	> 1:320
		NCT04333251	USA	115 (Exp: NA; Ctr: NA)	1-2 units of CP (250 mL/24h) *vs* BSC	>1:64
		NCT04355767	USA	206 (Exp: NA; Ctr: NA)	1-2 units of CP (200-600 mL) *vs* placebo	>1:80
		NCT04373460	USA	1344 (Exp: 772; Ctr : 772)	1 unit of CP (200-250 ml) vs. nonconvalescent plasma	≥ 1:320
		NCT04362176	USA	500 (Exp: 250; Ctr: 250)	1 unit of CP (250 ml at a rate of 500 mL/hour) vs. placebo	NA
		NCT04376034	USA	240 (Exp: NA; Ctr: NA)	1 (moderate) or 2 (severe) unit(s) of CP vs. BSC	NA
		NCT04377568	Canada	100 (Exp: NA; Ctr: NA)	10 mL/kg, up to 500 mL *vs* BSC	NA

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	Non critically ill patients	ChiCTR2000030702	China	50 (Exp: 25; Ctr:25)	NA *vs*. BSC	NA
		ChiCTR2000030929	China	80 (Exp: 30; Ctr:30)	NA *vs*. BSC	NA
		ChiCTR2000030010	China	100 (Exp: 50; Ctr: 50)	NA *vs*. BSC	NA
		NCT04332835	Colombia	80 (Exp: NA; Ctr: NA)	2 units of CP (250 mL/24h) *vs* BSC	NA
		NCT04345991	France	120 (Exp: NA; Ctr: NA)	up to 4 units of CP (200-220 ml each) *vs*. BSC	NA
		NCT04356534	Bahrain	40 (Exp: 20; Ctr: 20)	2 units of CP 200 ml each over 2 hours in 2 consecutive days *vs*. BSC	NA
		NCT04374526	Italy	182 (Exp: NA; Ctr: NA)	200 ml/d for 3 consecutive days *vs*. BSC	NA
		NCT04358783	Mexico	30 (Exp 20; Ctr 10)	1 unit (200 ml of CP) vs. BSC	NA
		NCT04345523	Spain	278 (Exp 139; Ctr: 139)	CP *vs*. BSC	NA
		NCT04364737	USA	300 (Exp: NA; Ctr: NA)	1-2 units (250 ml each) *vs*. iv placebo	NA
		NCT04361253	USA	220 (Exp: NA; Ctr: NA)	2 units of CP (250 ml each) within 24 hrs *vs*. nonconvalescent plasma	NA
		NCT04359810	USA	105 (Exp 70; Ctr 35)	1 unit (200-250 ml) of CP vs. nonconvalescent plasma	NA
		NCT04348656	Canada	1200 (Exp: NA; Ctr:	500 mL CP within 12 hours *vs*. BSC	NA

				NA)		
	Severe or critically ill patients	ChiCTR2000029850	China	20 (Exp: 10; Ctr: 10)	NA *vs*. BSC	NA
		ChiCTR2000030179	China	100 (Exp: 50; Ctr: 50)	NA *vs*. BSC	NA
		ChiCTR2000030627	China	30 (Exp: 15; Ctr: 15)	NA *vs*. BSC	NA
		ChiCTR2000029757	China	200 (Exp: 100; Ctr:100)	NA *vs*. BSC	NA
		NCT04346446	India	40 (Exp: NA; Ctr: NA)	1-3 unit (200 ml each) of CP vs. nonconvalescent plasma	NA

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