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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 used since early 1900s to treat emerging infectious disease : its efficacy was later associated with the evidence that polyclonal neutralizing antibodies can reduce duration of viremia. Recent large outbreaks of viral diseases for which effective antivirals or vaccines are still lacking has renewed 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)).

If an emerging agent induces neutralizing antibodies, then transfusion of convalescent blood products (CBP), especially convalescent plasma (CP), can be useful at passively carrying them (8). This approach has been used since 1900 and previous experiences have been reported elsewhere(9). CBPs are manufactured by collecting whole blood or apheresis plasma from a convalescent donor.

The main accepted mechanism of action for CBP therapy is clearance of viraemia, which typically happens 10–14 days after infection (10). 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) (11).

In the setting of respiratory viral infections, not only IgGs are relevant for protection. The lung requires specific antiviral IgG_{2a} for protection in terminal bronchioles and alveoli (12, 13), but secretory IgA, which is the main immunoglobulin isotype on mucosal surfaces, is also a key player. It is 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 pass into alveolar fluids (14).

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.

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Several data included in this review comes from preprints which have not passed peer-review yet, as acknowledged in the reference section.

CP donor recruitment strategies

Donor testing for neutralizing antibodies (or at least their surrogates in ELISA) is mandatory in upstream donor selection. Donor selection is generally based on neutralizing antibody titer as assessed with the plaque reduction neutralization test (PRNT) (15), which requires a viable isolate, replication-competent cell lines and skilled personnel. Since PRNT takes time to be set up 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, small CP case series (16, 17) and larger observational studies (18, 19) have suggested that ELISA ratios/indexes have very high correlation with PRNT titers. Current understanding of neutralization suggests that the virus-blocking effect is related to the amount of antibodies against different epitopes coating the virion, whose stoichiometry is in turn affected by antibody concentration and affinity.

The donor should preferably live in the same area as the intended recipient(s) to consider mutations of the target viral antigens. SARS-CoV2 S protein has already mutated after a few months of viral circulation, with one mutation (23403A>G single nucleotide polymorphism, corresponding to D614G amino acid change) outside the receptor-binding motif currently defining a dominant clade (20), and more missense mutations accumulating (21). It should be considered that preferring indigenous donors could represent a drawback in areas epidemic for other infectious diseases (e.g. malaria).

Three approaches are theoretically available to recruit CP donors, each having pros and cons. The least cost-effective approach is screening the general regular 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.

Alternatively, 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, whenever allowed by privacy regulations, is deploying calls to donate to positive cases under home-based quarantine: given the large numbers, some of them are likely to be regular donors, and home-based convalescence suggests they are fit enough to donate. Nevertheless, lessons from MERS suggest that patients with mild symptoms may develop low-titer antibodies (22), making antibody titration even more important in the population-wide and home-based approaches. Plasmas collected an average of 30 days after the onset of symptoms had undetectable half-maximal neutralizing titers in 18% (19).

A threshold for repeat donations should also be established as soon as banking has reached demand-offer equilibrium (23).

As recently suggested plasmapheresis could additionally benefit the convalescent COVID-19 donor by reducing its prothrombotic state via citrate-based anticoagulants and removal of high molecular weight viscous components(24).

In additional to interventional trials, in the USA at least 3 trials have been initiated 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 encouraged to better face next waves of the COVID19 pandemic.

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, 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 than with whole blood donations, 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. A very explorative approach is under investigation in a Chinese trial collecting immunoglobulins from convalescent donors by immunoadsorption (NCT04264858), which could be an alternative to plasma fractionation.

Technologies to virally reduce plasma (pathogen inactivation)

Although neither the US Food and Drug Agency (FDA)(25) nor the European Center for Disease Control are recommending pathogen reduction technologies (PRT) for CP (26), 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 (27). 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 (28)

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(Theraflex®), amotosalen (S-59) + ultraviolet A (29) (Intercept®), and riboflavin + ultraviolet B (30) (Mirasol®). These methods do not affect immunoglobulin activity.

Fatty acids are also an option. In 2002 it was reported that caprylic acid (31) and octanoic acid (32) were as effective as S/D at inactivating enveloped viruses.

Heat-treatment of plasma has been used in the past (33, 34) but goes with the risk of aggregation of immunoglobulins (35, 36).

Pooling

Figure 1 represents how CP and IVIG can be obtained under modern fractionation procedures. As per CP, 2 approaches can be pursued.

Large-pool products

Pharmaceutical-grade facilities typically pool 100/2500 donors to manufacture S/D-inactivated plasma. Intravenous immunoglobulins (IVIG) are similarly prepared from pools of 2000–4000 L of plasma (or 100-1000 L in the case of hyperimmune IVIG) (37, 38). Such size can be hardly matched from CP donors and facilities rearrangement poses hard GMP issues (38).

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. An “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 (39) and

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immunoglobulins (6-fold enrichment) (40). The same disposable bag system has also been combined with S/D reduction (27).

CP banking

CP can be either frozen or transfused as a fresh product. Aliquots can be easily achieved with modern PRT kits. Banking at temperature below -25˚C (according to EDQM guidelines for ordinary plasma for clinical use (41)) 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. A single cycle of freezing and thawing does not significatively affect quantity or function of immunoglobulins (42). Given the scarcity of blood group AB donors, several authors have recommended titration of anti-A and anti-B isoagglutinins and transfusion of low-titer (< 1:32) non-ABO compatible CP units to AB recipients(23).

Lessons from SARS

SARS-CoV RNA was found in respiratory specimens from one third of patients for up to 4 weeks following symptoms (43). SARS-specific antibodies usually persist for 2 years(44), and decline in prevalence and titers occurs in the third year (45). Convalescent anti-SARS immunoglobulins were manufactured on a small scale (8, 46). 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 (47). 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 (48). Amotosalen photochemical inactivation of apheresis platelet concentrates demonstrated a >6.2 log10 mean reduction of SARS-CoV (49). Theraflex˚ reduces infectivity of SARS-CoV in plasma (50). Heating at 60°C for 15-30 minutes reduces SARS-CoV from plasma without cells (51), while 60°C for 10 hours is required for plasma products (52). In addition, SARS-CoV was found to be sensitive to S/D (51, 53).

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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 antibody titers, making CP collection challenging in MERS convalescents (54). 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 (22). CP with a PRNT titre ≥1:80 provide clinical benefit in MERS (55). A case of TRALI following CP transfusion in a patient with MERS was reported (56, 57). MERS-CoV load in plasma was reduced by Theraflex® (58), Intercept® (59), Mirasol® (60), and 56°C heating for 25 minutes (61) : 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, 62), several authors suggested CP as a potential therapeutic agent (63, 64). Of interest, the most critically ill patients show prolonged viremia (strongly correlated with serum IL-6 levels) (65), 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 (62), mandating SARS-CoV2 RNA screening in CP donors. Appearance of serum IgM and IgA antibody in COVID-19 occurs since 5 days after symptom onset, while IgG is detected since day 14 (66, 67). IgG are universally detected after 20 days (68, 69). Severely ill female patients generate IgG earlier and in higher titers (70): the greatest part of the neutralizing antibody response has been shown to be associated with the IgG_1 and IgG_3 subclass(18, 71). Duration of anti-SARS-CoV2 antibodies in plasma remains unknown, though for other betacoronaviruses immunity typically lasts 6-12 months (72). So, in the vast majority of countries, a suitable donor could donate 600 ml plasma (equivalent to 3 therapeutic doses under most current trials) 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: this could suggest that the majority of convalescent

donors are best sought after in the general population, although specific studies on antibody titers in asymptomatic patients are still missing.

SARS-CoV2 is reduced by > 3.4 logs by Mirasol® (73) (and likely by other PRT): nevertheless, SARS-CoV2 vRNA is detectable at low viral loads in a minority of serum samples collected in acute infection, but is not associated with infectious SARS-CoV-2 (74).

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(75).

In an early 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 PRNT 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 (17).

Another Chinese pilot study (ChiCTR2000030046) of 10 critically ill patients showed that one dose of 200 mL CP with neutralizing antibody titers > 1:640 resulted in an undetectable viral load in 7 patients, radiological and clinical improvement (16).

A third series of 6 cases with COVID19 pneumonia in Wuhan showed that a single 200 ml dose of CP (with anti-S antibodies titred by chemiluminescent immunoassay (CLIA) only) administered at a late stage led to viral clearance in 2 patients and radiological resolution in 5 patients (76). Pei *et al* reported successful treatment of 2 out of 3 patients with 200-500 ml doses of CP (77). Recovery from mechanical ventilation was also reported by Zhang *et al* in a single patient after CP titrated with anti-N protein ELISA (78). No improve in mortality despite viral clearance were 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 (79).

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 (80), and CP plus remdesivir was reported for the treatment of a critically ill obstetric patient in USA (81).

In the first retrospective, randomized controlled trial published to date, 39 severe COVID-19 patients in New York were transfused with 2 units of ABO-type matched CP with anti-Spike antibody titers ≥1:320 (measured by a two-step Spike protein-directed ELISA). CP recipients were more likely than control patients to not increase their supplemental oxygen requirements by post-transfusion day 14 (OR 0.86), but survival only improved for non-intubated patients (HR 0.19)(82).

Table 1 lists the other ongoing CP trials in COVID-19 patients collected from different web portals. The US have developed a specific platform 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/) . At the same time, in the USA an Expanded Access Program (EAP) has been approved by FDA and coordinated by Mayo University, and has led to treatment of more than 8,800 patients as of May 11, 2020 (https://www.uscovidplasma.org). Preliminary report on the first 5,000 patients (66% from intensive care unit) confirm safety (< 1% severe adverse events and 14.9% mortality at 14 days) and suggest benefit when compared to historical cohorts (83): donor titers were not disclosed and eventually some donations were not titred before reinfusion. Largely similar data have been reported from a 25 patients-case series from Houston, where CP has been used as emerging investigational new drug (eIND)(84).

Typically, up to 2 doses 200 ml each are administered at least 12 hours apart, with infusion rate 100 to 200 mL/hour. The cumulative dose should be targeted according to body weight and antibody titer (23). Several authors have suggested plasma exchange with CP rather than just CP transfusion in order to clear proinflammatory cytokines from bloodstream(85), but to date no trial is investigating such combined approach.

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Unfortunately, most trial in Westernized countries (contrary to 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 prothrombotic nature of COVID-19 pathology (see paragraph below). 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 merged with Biotest, BPL, LFB, Octpharma and CSL Behring into the "Convalescent Plasma Coalition" (86); Kedrion and Kamada joint ventures (16)).

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, 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.

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 (87) – or by some individuals. In addition, there is a now a recognized risk of hepatitis E the within UK blood donor population (88), most likely due to the consumption of poorly cooked pork products (89, 90), for which screening has only relatively recently been initiated (91). 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. Respiratory betacoronaviruses produce only a mild and transient viremia. With SARS-CoV, limited replication in lymphocytes (92) 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). Preliminary reports have shown SARS-CoV2 viremia persists only in critically ill patients (65).

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.

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 (93, 94), 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"). ELISA discriminating the difference between total and RBD-binding antibodies could be useful to inspect occurrence of ADE. Genetic polymorphisms (e.g. FcγRIIa (95)) 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 (96-99), including neutralizing antibodies (100,

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101) ; 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 cross-reacting coronaviruses 229E or OC43, or anyway have low-affinity anti-coronavirus IgG (102, 103)); 3) in SARS, occurrence of ADE has been shown *in vitro* at low antibody titers (104), and in patients high IgG titres and early seroconversion correlate with disease severity(105). Overall, these findings pose concerns on usage of low-titer CP units (106). Another evidence is the high level of afucosylated IgG against S protein, facilitating FcR binding, that are produced in the most severely ill patients (107, 108).

A last, COVID-specific concern is worsening of the underlying coagulopathy(109) from clotting factors in transfused plasma (not only CP but also nonconvalescent plasma in control arms) : since this has not been reported to date, it remains a theoretical concern.

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 (110), likely stemming from recent infection with other human betacoronavirus (103). Accordingly, IVIg lead to clinical and radiological recovery in 3 severe Chinese COVID-19 patients(111) 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 (112), 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 (113). Such binding could opsonize virions and induce complement-mediated neutralization (114). 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 (115) and SARS-CoV2 (116) S protein. Several publications showed that the odds ratio for acquiring COVID-19 is higher in blood group A than in blood group 0 (117-120). 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 (121, 122). Although alternative explanations exist(123), studies are hence ongoing to evaluate correlations between isoagglutinin titers and outcome in blood group 0 and B patients. If confirmed, while preserving ABO match compatibility, blood group 0 and B donors for CP in COVID-19 could be preferred, and to titre their anti-A isoagglutinins.

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).

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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 May 15, 2020), NIH ClinicalTrials database (accessed online at www.clinicaltrials.gov on May 15 2020), and Cytel Global Coronavirus COVID-19 Clinical Trial Tracker (accessed online at www.covid-trials.org on May 15 2020). BSC: best supportive care; NA: not available; Exp: experimental group; Ctr: control group; EAP: expanded access program.

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

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		NCT04343755	USA	55	NA	> 1:64
		NCT04360486		EAP	NA	NA
		NCT04354831		131	1-2 units of CP (<7 ml/kg adjusted IBW)	NA
		NCT04355897		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	NCT04348877	Egypt	20	1 400 ml unit of CP	NA
		NCT04321421	Italy	49	3 units of CP (250-300 mL/48h)	NA
		NCT04346589		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
		NCT04352751	Pakistan	2000	children < 35 kg: 15 ml/kg over 4-6 hrs;	NA

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					adults: < 450 - 500 ml over 4-6 hours	
		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
		NCT04374370		EAP	1-2 units (200-400 mL per unit), not to exceed 550 mL total	NA
		NCT04358211		EAP		> 160
		NCT04363034		EAP up to 100		NA
		NCT04372368		EAP up to 150		NA
		NCT04340050		10	1 unit of CP (300 ml)	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	NCT04377568	Canada	100 (Exp: NA; Ctr: NA)	10 mL/kg, up to 500 mL *vs* BSC	NA
		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*	NA

					nonconvalescent plasma	
		NCT04374487	India	100 (Exp: NA; Ctr: NA)	up to 3 200 ml doses of CP 24 hrs apart *vs* BSC	> 1:40
		NCT04346446		40(Exp: NA; Ctr: NA)	1-3 units (200 ml) of CP vs. nonconvalescent plasma	NA
		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		115 (Exp: NA; Ctr: NA)	1-2 units of CP (250 mL/24h) *vs* BSC	>1:64
		NCT04355767		206 (Exp: NA; Ctr: NA)	1-2 units of CP (200-600 mL) *vs* placebo	>1:80
		NCT04373460		1344 (Exp: 772; Ctr : 772)	1 unit of CP (200-250 ml) vs. nonconvalescent plasma	≥ 1:320
		NCT04362176		500 (Exp: 250; Ctr: 250)	1 unit of CP (250 ml at a rate of 500 mL/hour) vs. placebo	NA

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		NCT04376034		240 (Exp: NA; Ctr: NA)	1 (moderate) or 2 (severe) unit(s) of CP vs. BSC	NA
	Non critically ill patients					
		NCT04356534	Bahrain	40 (Exp: 20; Ctr: 20)	2 units of CP 200 ml each over 2 hours in 2 consecutive days *vs*. BSC	NA
		NCT04348656	Canada	1200 (Exp: NA; Ctr: NA)	500 mL CP within 12 hours *vs*. BSC	NA
		ChiCTR2000030702	China	50 (Exp: 25; Ctr:25)	NA *vs*. BSC	NA
		ChiCTR2000030929		80 (Exp: 30; Ctr:30)	NA *vs*. BSC	NA
		ChiCTR2000030010		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
		NCT04374526	Italy	182 (Exp: NA; Ctr: NA)	200 ml/d for 3 consecutive days *vs*. BSC	NA
		NCT04393727	Italy	126 (Exp: 63; Ctr: 63)	1 unit (200 ml) of CP 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

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		NCT04364737	USA	300 (Exp: NA; Ctr: NA)	1-2 units (250 ml each) *vs*. iv placebo	NA
		NCT04361253		220 (Exp: NA; Ctr: NA)	2 units of CP (250 ml each) within 24 hrs *vs*. nonconvalescent plasma	NA
		NCT04359810		105 (Exp 70; Ctr 35)	1 unit (200-250 ml) of CP vs. nonconvalescent plasma	NA
	Severe or critically ill patients	ChiCTR2000029850	China	20 (Exp: 10; Ctr: 10)	NA *vs*. BSC	NA
		ChiCTR2000030179		100 (Exp: 50; Ctr: 50)	NA *vs*. BSC	NA
		ChiCTR2000030627		30 (Exp: 15; Ctr: 15)	NA *vs*. BSC	NA
		ChiCTR2000029757		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
		NCT04385043	Italy	400 (Exp: 200; Ctr : 200)	NA vs BSC	NA
		NCT04381858	Mexico	500 (Exp : 340: Ctr: 160)	2 units (200 ml each(of CP vs polyclonal IVIg 0.3 gr/kg/day (5 doses)	NA

References

1. Guarner J, Hale GL. 2019. Four human diseases with significant public health impact caused by mosquito-borne flaviviruses: West Nile, Zika, dengue and yellow fever. Semin Diagn Pathol 36:170-176.
2. Vairo F, Haider N, Kock R, Ntoumi F, Ippolito G, Zumla A. 2019. Chikungunya: Epidemiology, Pathogenesis, Clinical Features, Management, and Prevention. Infect Dis Clin North Am 33:1003-1025.
3. Vogel OA, Manicassamy B. 2020. Broadly Protective Strategies Against Influenza Viruses: Universal Vaccines and Therapeutics. Front Microbiol 11:135.
4. Hoenen T, Groseth A, Feldmann H. 2019. Therapeutic strategies to target the Ebola virus life cycle. Nat Rev Microbiol 17:593-606.
5. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwosh HA, Walmsley SL, Mazzulli T, Avendano M, Derkach P, Ephtimios IE, Kitai I, Mederski BD, Shadowitz SB, Gold WL, Hawryluck LA, Rea E, Chenkin JS, Cescon DW, Poutanen SM, Detsky AS. 2003. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. Jama 289:2801-9.
6. Bermingham A, Chand MA, Brown CS, Aarons E, Tong C, Langrish C, Hoschler K, Brown K, Galiano M, Myers R, Pebody RG, Green HK, Boddington NL, Gopal R, Price N, Newsholme W, Drosten C, Fouchier RA, Zambon M. 2012. Severe respiratory illness caused by a novel coronavirus, in a patient transferred to the United Kingdom from the Middle East, September 2012. Euro Surveill 17:20290.
7. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, Zhao X, Huang B, Shi W, Lu R, Niu P, Zhan F, Ma X, Wang D, Xu W, Wu G, Gao GF, Tan W. 2020. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 382:727-733.
8. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, Makki S, Rooney KD, Nguyen-Van-Tam JS, Beck CR. 2015. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 211:80-90.
9. Casadevall A, Pirofski LA. 2020. The convalescent sera option for containing COVID-19. J Clin Invest 130:1545-1548.
10. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, Chan P, Wong KC, Leung CB, Cheng G. 2005. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 24:44-6.
11. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. 2006. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? Ann Intern Med 145:599-609.
12. Fazekas G, Rosenwirth B, Dukor P, Gergely J, Rajnavolgyi E. 1994. IgG isotype distribution of local and systemic immune responses induced by influenza virus infection. Eur J Immunol 24:3063-7.
13. Mostov KE. 1994. Transepithelial transport of immunoglobulins. Annu Rev Immunol 12:63-84.
14. Roopenian DC, Akilesh S. 2007. FcRn: the neonatal Fc receptor comes of age. Nat Rev Immunol 7:715-25.
15. Franchini M, Marano G, Velati C, Pati I, Pupella S, Liumbruno GM. 2020. Operational protocol for donation of anti-COVID-19 convalescent plasma in Italy. Vox Sang doi:10.1111/vox.12940.
16. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X. 2020. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences doi:10.1073/pnas.2004168117:202004168.
17. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L. 2020. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA doi:10.1001/jama.2020.4783.

18. Suthar MS, Zimmerman M, Kauffman R, Mantus G, Linderman S, Vanderheiden A, Nyhoff L, Davis C, Adekunle S, Affer M, Sherman M, Reynolds S, Verkerke H, Alter DN, Guarner J, Bryksin J, Horwath M, Arthur C, Saakadze N, Smith GH, Edupuganti S, Scherer EM, Hellmeister K, Cheng A, Morales JA, Neish AS, Stowell SR, Frank F, Ortlund E, Anderson E, Menachery V, Rouphael N, Metha A, Stephens DS, Ahmed R, Roback J, Wrammert J. 2020. Rapid generation of neutralizing antibody responses in COVID-19 patients. medRxiv doi:10.1101/2020.05.03.20084442:2020.05.03.20084442.
19. Robbiani DF, Gaebler C, Muecksch F, Cetrulo Lorenzi J, Wang Z, Cho A, Agudelo M, Barnes C, Finkin S, Hagglof T, Oliveira T, Viant C, Hurley A, Millard K, Kost R, Cipolla M, Gazumyan A, Gordon K, Bianchini F, Chen S, Ramos V, Patel R, Dizon J, Shimeliovich I, Mendoza P, Hartweger H, Nogueira L, Pack M, Horowitz J, Schmidt F, Weisblum Y, Hoffmann H-H, Michailidis E, Ashbrook A, Waltari EF, Pak J, Huey-Tubman K, Koranda N, Hoffman P, West A, Rice C, Hatziioannou T, Bjorkman P, Bieniasz P, Caskey M, Nussenzweig M. 2020. Convergent Antibody Responses to SARS-CoV-2 Infection in Convalescent Individuals. bioRxiv doi:10.1101/2020.05.13.092619:2020.05.13.092619.
20. Koyama T, Weeraratne D, Snowdon JL, Parida L. 2020. Emergence of Drift Variants That May Affect COVID-19 Vaccine Development and Antibody Treatment. Pathogens 9.
21. Phelan J, Deelder W, Ward D, Campino S, Hibberd ML, Clark TG. 2020. Controlling the SARS-CoV-2 outbreak, insights from large scale whole genome sequences generated across the world. bioRxiv doi:10.1101/2020.04.28.066977:2020.04.28.066977.
22. Arabi YM, Hajeer AH, Luke T, Raviprakash K, Balkhy H, Johani S, Al-Dawood A, Al-Qahtani S, Al-Omari A, Al-Hameed F, Hayden FG, Fowler R, Bouchama A, Shindo N, Al-Khairy K, Carson G, Taha Y, Sadat M, Alahmadi M. 2016. Feasibility of Using Convalescent Plasma Immunotherapy for MERS-CoV Infection, Saudi Arabia. Emerg Infect Dis 22:1554-61.
23. Knudson CM, Jackson JB. COVID-19 convalescent plasma: phase 2. Transfusion n/a.
24. Seghatchian J, Lanza F. 2020. Convalescent plasma, an apheresis research project targeting and motivating the fully recovered COVID 19 patients: A rousing message of clinical benefit to both donors and recipients alike. Transfus Apher Sci doi:10.1016/j.transci.2020.102792:102792.
25. FDA. 2020. Recommendations for Investigational COVID-19 Convalescent Plasma. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. Accessed
26. Commission E. 2020. Guidance on collection, testing, processing, storage, distribution and monitored use Brussels.
27. El-Ekiaby M, Sayed MA, Caron C, Burnouf S, El-Sharkawy N, Goubran H, Radosevich M, Goudemand J, Blum D, De Melo L, Soulié V, Adam J, Burnouf T. 2010. Solvent-detergent filtered (S/D-F) fresh frozen plasma and cryoprecipitate minipools prepared in a newly designed integral disposable processing bag system. Transfusion Medicine 20:48-61.
28. Wong HK, Lee CK, Hung IF, Leung JN, Hong J, Yuen KY, Lin CK. 2010. Practical limitations of convalescent plasma collection: a case scenario in pandemic preparation for influenza A (H1N1) infection. Transfusion 50:1967-71.
29. Singh Y, Sawyer LS, Pinkoski LS, Dupuis KW, Hsu JC, Lin L, Corash L. 2006. Photochemical treatment of plasma with amotosalen and long-wavelength ultraviolet light inactivates pathogens while retaining coagulation function. Transfusion 46:1168-1177.
30. Bihm DJ, Ettinger A, Buytaert-Hoefen KA, Hendrix BK, Maldonado-Codina G, Rock G, Giclas PC, Goodrich RP. 2010. Characterization of plasma protein activity in riboflavin and UV light-treated fresh frozen plasma during 2 years of storage at −30°C. Vox Sanguinis 98:108-115.
31. Korneyeva M, Hotta J, Lebing W, Rosenthal RS, Franks L, Petteway SR. 2002. Enveloped Virus Inactivation by Caprylate: A Robust Alternative to Solvent-Detergent Treatment in Plasma Derived Intermediates. Biologicals 30:153-162.
32. Dichtelmüller H, Rudnick D, Kloft M. 2002. Inactivation of Lipid Enveloped Viruses by Octanoic Acid Treatment of Immunoglobulin Solution. Biologicals 30:135-142.
33. Goubran HA, Burnouf T, Radosevich M. 2000. Virucidal heat-treatment of single plasma units: a potential approach for developing countries. Haemophilia 6:597-604.

34. Watt G, Kantipong P, Jongsakul K, de Souza M, Burnouf T. 2001. Passive transfer of scrub typhus plasma to patients with AIDS: a descriptive clinical study. Qjm 94:599-607.
35. Vittecoq D, Mattlinger B, Barre-Sinoussi F, Courouce AM, Rouzioux C, Doinel C, Bary M, Viard JP, Bach JF, Rouger P, Lefrere JJ. 1992. Passive Immunotherapy in AIDS: A Randomized Trial of Serial Human Immunodeficiency Virus-Positive Transfusions of Plasma Rich in p24 Antibodies versus Transfusions of Seronegative Plasma. The Journal of Infectious Diseases 165:364-368.
36. Vittecoq D, Chevret S, Morand-Joubert L, Heshmati F, Audat F, Bary M, Dusautoir T, Bismuth A, Viard JP, Barré-Sinoussi F. 1995. Passive immunotherapy in AIDS: a double-blind randomized study based on transfusions of plasma rich in anti-human immunodeficiency virus 1 antibodies vs. transfusions of seronegative plasma. Proceedings of the National Academy of Sciences 92:1195-1199.
37. Radosevich M, Burnouf T. 2010. Intravenous immunoglobulin G: trends in production methods, quality control and quality assurance. Vox Sanguinis 98:12-28.
38. WHO. 2007. Annex 4. Recommendations for the collection, quality control and regulation of human plasma for fractionation. WHO Tech Rep Ser 941:189-264.
39. El-Ekiaby M, Radosevich M, Goubran H, El Sayed M, Burnouf T. 2009. New methods of plasma fractionation – a presentation of the 'mini-pool' fractionation procedure developed in Egypt. ISBT Science Series 4:99-106.
40. El-Ekiaby M, Vargas M, Sayed M, Gorgy G, Goubran H, Radosevic M, Burnouf T. 2015. Minipool caprylic acid fractionation of plasma using disposable equipment: a practical method to enhance immunoglobulin supply in developing countries. PLoS neglected tropical diseases 9:e0003501-e0003501.
41. Healthcare EDftQoMa. 2017. 19th Edition of the Guide to the Preparation, Use and Quality Assurance of Blood Components.
42. Pinsky NA, Huddleston JM, Jacobson RM, Wollan PC, Poland GA. 2003. Effect of multiple freeze-thaw cycles on detection of measles, mumps, and rubella virus antibodies. Clinical and diagnostic laboratory immunology 10:19-21.
43. Xu D, Zhang Z, Jin L, Chu F, Mao Y, Wang H, Liu M, Wang M, Zhang L, Gao GF, Wang FS. 2005. Persistent shedding of viable SARS-CoV in urine and stool of SARS patients during the convalescent phase. Eur J Clin Microbiol Infect Dis 24:165-71.
44. Liu W, Fontanet A, Zhang PH, Zhan L, Xin ZT, Baril L, Tang F, Lv H, Cao WC. 2006. Two-year prospective study of the humoral immune response of patients with severe acute respiratory syndrome. J Infect Dis 193:792-5.
45. Wu L-P, Wang N-C, Chang Y-H, Tian X-Y, Na D-Y, Zhang L-Y, Zheng L, Lan T, Wang L-F, Liang G-D. 2007. Duration of antibody responses after severe acute respiratory syndrome. Emerging infectious diseases 13:1562-1564.
46. Zhang Z, Xie Y-W, Hong J, Zhang X, Kwok SY, Huang X, Wong SW, Wong B-L, Group S. 2005. Purification of severe acute respiratory syndrome hyperimmune globulins for intravenous injection from convalescent plasma. Transfusion 45:1160-1164.
47. Yeh K, Chiueh T, Siu L. 2005. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother 56:919-22.
48. Soo YO, Cheng Y, Wong R, Hui DS, Lee CK, Tsang KK, Ng MH, Chan P, Cheng G, Sung JJ. 2004. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 10:676-8.
49. Pinna D, Sampson-Johannes A, Clementi M, Poli G, Rossini S, Lin L, Vicenzi E. 2005. Amotosalen photochemical inactivation of severe acute respiratory syndrome coronavirus in human platelet concentrates. Transfus Med 15:269-76.
50. Eickmann M, Gravemann U, Handke W, Tolksdorf F, Reichenberg S, Muller TH, Seltsam A. 2020. Inactivation of three emerging viruses - severe acute respiratory syndrome coronavirus, Crimean-Congo haemorrhagic fever virus and Nipah virus - in platelet concentrates by ultraviolet C light and in plasma by methylene blue plus visible light. Vox Sang doi:10.1111/vox.12888.

51. Darnell ME, Taylor DR. 2006. Evaluation of inactivation methods for severe acute respiratory syndrome coronavirus in noncellular blood products. Transfusion 46:1770-7.
52. Yunoki M, Urayama T, Yamamoto I, Abe S, Ikuta K. 2004. Heat sensitivity of a SARS-associated coronavirus introduced into plasma products. Vox Sang 87:302-3.
53. Rabenau HF, Biesert L, Schmidt T, Bauer G, Cinatl J, Doerr HW. 2005. SARS-coronavirus (SARS-CoV) and the safety of a solvent/detergent (S/D) treated immunoglobulin preparation. Biologicals 33:95-9.
54. Choe PG, Perera R, Park WB, Song KH, Bang JH, Kim ES, Kim HB, Ko LWR, Park SW, Kim NJ, Lau EHY, Poon LLM, Peiris M, Oh MD. 2017. MERS-CoV Antibody Responses 1 Year after Symptom Onset, South Korea, 2015. Emerg Infect Dis 23:1079-1084.
55. Ko JH, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, Kim YJ, Park JK, Chung CR, Kang ES, Cho D, Muller MA, Drosten C, Kang CI, Chung DR, Song JH, Peck KR. 2018. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther 23:617-622.
56. Chun S, Chung CR, Ha YE, Han TH, Ki CS, Kang ES, Park JK, Peck KR, Cho D. 2016. Possible Transfusion-Related Acute Lung Injury Following Convalescent Plasma Transfusion in a Patient With Middle East Respiratory Syndrome. Ann Lab Med 36:393-5.
57. Arabi Y, Balkhy H, Hajeer AH, Bouchama A, Hayden FG, Al-Omari A, Al-Hameed FM, Taha Y, Shindo N, Whitehead J, Merson L, AlJohani S, Al-Khairy K, Carson G, Luke TC, Hensley L, Al-Dawood A, Al-Qahtani S, Modjarrad K, Sadat M, Rohde G, Leport C, Fowler R. 2015. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. Springerplus 4:709.
58. Eickmann M, Gravemann U, Handke W, Tolksdorf F, Reichenberg S, Muller TH, Seltsam A. 2018. Inactivation of Ebola virus and Middle East respiratory syndrome coronavirus in platelet concentrates and plasma by ultraviolet C light and methylene blue plus visible light, respectively. Transfusion 58:2202-2207.
59. Hindawi SI, Hashem AM, Damanhouri GA, El-Kafrawy SA, Tolah AM, Hassan AM, Azhar EI. 2018. Inactivation of Middle East respiratory syndrome-coronavirus in human plasma using amotosalen and ultraviolet A light. Transfusion 58:52-59.
60. Keil SD, Bowen R, Marschner S. 2016. Inactivation of Middle East respiratory syndrome coronavirus (MERS-CoV) in plasma products using a riboflavin-based and ultraviolet light-based photochemical treatment. Transfusion 56:2948-2952.
61. Leclercq I, Batejat C, Burguiere AM, Manuguerra JC. 2014. Heat inactivation of the Middle East respiratory syndrome coronavirus. Influenza Other Respir Viruses 8:585-6.
62. Zhou F, Yu T, Du R, Fan G. 2020. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.
63. Casadevall A, Pirofski L-a. 2020. The convalescent sera option for containing COVID-19. The Journal of Clinical Investigation 130.
64. Chen L, Xiong J, Bao L, Shi Y. 2020. Convalescent plasma as a potential therapy for COVID-19. Lancet Inf Dis doi:https://doi.org/10.1016/S1473-3099(20)30141-9.
65. Chen X, Zhao B, Qu Y, Chen Y, Xiong J, Feng Y, Men D, Huang Q, Liu Y, Yang B, Ding J, Li F. 2020. Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. medRxiv doi:10.1101/2020.02.29.20029520:2020.02.29.20029520.
66. Guo L, Ren L, Yang S, Xiao M, Chang D, Yang F, Dela Cruz CS, Wang Y, Wu C, Xiao Y, Zhang L, Han L, Dang S, Xu Y, Yang Q, Xu S, Zhu H, Xu Y, Jin Q, Sharma L, Wang L, Wang J. 2020. Profiling Early Humoral Response to Diagnose Novel Coronavirus Disease (COVID-19). Clinical Infectious Diseases doi:10.1093/cid/ciaa310.
67. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, Wang X, Yuan J, Li T, Li J, Qian S, Hong C, Wang F, Liu Y, Wang Z, He Q, Li Z, He B, Zhang T, Ge S, Liu L, Zhang J, Xia N, Zhang Z. 2020. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. medRxiv doi:10.1101/2020.03.02.20030189:2020.03.02.20030189.

68. Long Q-x, Deng H-j, Chen J, Hu J, Liu B-z, Liao P, Lin Y, Yu L-h, Mo Z, Xu Y-y, Gong F, Wu G-c, Zhang X-x, Chen Y-k, Li Z-j, Wang K, Zhang X-l, Tian W-g, Niu C-c, Yang Q-j, Xiang J-l, Du H-x, Liu H-w, Lang C, Luo X-h, Wu S-b, Cui X-p, Zhou Z, Wang J, Xue C-j, Li X-f, Wang L, Tang X-j, Zhang Y, Qiu J-f, Liu X-m, Li J-j, Zhang D-c, Zhang F, Cai X-f, Wang D, Hu Y, Ren J-h, Tang N, Liu P, Li Q, Huang A-l. 2020. Antibody responses to SARS-CoV-2 in COVID-19 patients: the perspective application of serological tests in clinical practice. medRxiv doi:10.1101/2020.03.18.20038018:2020.03.18.20038018.
69. Long Q-X, Liu B-Z, Deng H-J, Wu G-C, Deng K, Chen Y-K, Liao P, Qiu J-F, Lin Y, Cai X-F, Wang D-Q, Hu Y, Ren J-H, Tang N, Xu Y-Y, Yu L-H, Mo Z, Gong F, Zhang X-L, Tian W-G, Hu L, Zhang X-X, Xiang J-L, Du H-X, Liu H-W, Lang C-H, Luo X-H, Wu S-B, Cui X-P, Zhou Z, Zhu M-M, Wang J, Xue C-J, Li X-F, Wang L, Li Z-J, Wang K, Niu C-C, Yang Q-J, Tang X-J, Zhang Y, Liu X-M, Li J-J, Zhang D-C, Zhang F, Liu P, Yuan J, Li Q, Hu J-L, Chen J, et al. 2020. Antibody responses to SARS-CoV-2 in patients with COVID-19. Nature Medicine doi:10.1038/s41591-020-0897-1.
70. Zeng F, Dai C, Cai P, Wang J, Xu L, Li J, Hu G, Wang L. 2020. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between gender. medRxiv doi:10.1101/2020.03.26.20040709:2020.03.26.20040709.
71. Amanat F, Stadlbauer D, Strohmeier S, Nguyen T, Chromikova V, McMahon M, Jiang K, Asthagiri-Arunkumar G, Jurczyszak D, Polanco J, Bermudez-Gonzalez M, Kleiner G, Aydillo T, Miorin L, Fierer D, Lugo LA, Milunka Kojic E, Stoever J, Liu STH, Cunningham-Rundles C, Felgner PL, Caplivski D, Garcia-Sastre A, Cheng A, Kedzierska K, Vapalahti O, Hepojoki J, Simon V, Krammer F, Moran T. 2020. A serological assay to detect SARS-CoV-2 seroconversion in humans. medRxiv doi:10.1101/2020.03.17.20037713:2020.03.17.20037713.
72. Chan KH, Cheng VC, Woo PC, Lau SK, Poon LL, Guan Y, Seto WH, Yuen KY, Peiris JS. 2005. Serological responses in patients with severe acute respiratory syndrome coronavirus infection and cross-reactivity with human coronaviruses 229E, OC43, and NL63. Clin Diagn Lab Immunol 12:1317-21.
73. Keil SD, Ragan I, Yonemura S, Hartson L, Dart NK, Bowen R. 2020. Inactivation of severe acute respiratory syndrome coronavirus 2 in plasma and platelet products using a riboflavin and ultraviolet light-based photochemical treatment. Vox Sang doi:10.1111/vox.12937.
74. Andersson M, Arancibia - Carcamo CV, Auckland K, Baillie JK, Barnes E, Beneke T, Bibi S, Carroll M, Crook D, Dingle K, Dold C, Downs LO, Dunn L, Eyre DW, Gilbert Jaramillo J, Harvala Simmonds H, Hoosdally S, Ijaz S, James T, James W, Jeffery K, Justice A, Klenerman P, Knight JC, Knight M, Liu X, Lumley SF, Matthews PC, McNaughton AL, Mentzer AJ, Mongkolsapaya J, Oakley S, Oliveira MS, Peto T, Ploeg RJ, Ratcliff J, Roberts DJ, Rudkin J, Screaton G, Semple MG, Skelley DT, Simmonds P, Stoesser N, Turtle L, Wareing S, Zambon M. 2020. SARS-CoV-2 RNA detected in blood samples from patients with COVID-19 is not associated with infectious virus. doi:10.1101/2020.05.21.20105486 %J medRxiv:2020.05.21.20105486.
75. Barone P, DeSimone RA. 2020. Convalescent plasma to treat coronavirus disease 2019 (COVID-19): considerations for clinical trial design. Transfusion doi:10.1111/trf.15843.
76. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, Xia X, Lv T. 2020. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. J Med Virol doi:10.1002/jmv.25882.
77. Pei S, Yuan X, Zhimin Zhang Z, Run Yao R, Xie Y, Minxue Shen M, Bijuan Li B, Chen X, Yin M. 2020. Convalescent Plasma to Treat COVID-19: Chinese Strategy and Experiences. doi:10.1101/2020.04.07.20056440 %J medRxiv:2020.04.07.20056440.
78. Zhang L, Pang R, Xue X, Bao J, Ye S, Dai Y, Zheng Y, Fu Q, Hu Z, Yi Y. 2020. Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19. Aging (Albany NY) 12.
79. Zeng Q-L, Yu Z-J, Gou J-J, Li G-M, Ma S-H, Zhang G-F, Xu J-H, Lin W-B, Cui G-L, Zhang M-M, Li C, Wang Z-S, Zhang Z-H, Liu Z-S. 2020. Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. The Journal of Infectious Diseases doi:10.1093/infdis/jiaa228.
80. Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, Jeong SJ, Kim JH, Ku NS, Yeom JS, Roh J, Ahn MY, Chin BS, Kim YS, Lee H, Yong D, Kim HO, Kim S, Choi JY. 2020. Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea. J Korean Med Sci 35:e149.

81. Anderson J, Schauer J, Bryant S, Graves CR. 2020. The use of convalescent plasma therapy and remdesivir in the successful management of a critically ill obstetric patient with novel coronavirus 2019 infection: A case report. Case Rep Womens Health doi:10.1016/j.crwh.2020.e00221:e00221.
82. Liu STH, Lin H-M, Baine I, Wajnberg A, Gumprecht JP, Rahman F, Rodriguez D, Tandon P, Bassily-Marcus A, Bander J, Sanky C, Dupper A, Zheng A, Altman DR, Chen BK, Krammer F, Mendu DR, Firpo-Betancourt A, Levin MA, Bagiella E, Casadevall A, Cordon-Cardo C, Jhang JS, Arinsburg SA, Reich DL, Aberg JA, Bouvier NM. 2020. Convalescent plasma treatment of severe COVID-19: A matched control study. doi:10.1101/2020.05.20.20102236 %J medRxiv:2020.05.20.20102236.
83. Joyner M, Wright RS, Fairweather D, Senefeld J, Bruno K, Klassen S, Carter R, Klompas A, Wiggins C, Shepherd JR, Rea R, Whelan E, Clayburn A, Spiegel M, Johnson P, Lesser E, Baker S, Larson K, Ripoll Sanz J, Andersen K, Hodge D, Kunze K, Buras M, Vogt M, Herasevich V, Dennis J, Regimbal R, Bauer P, Blair J, van Buskirk C, Winters J, Stubbs J, Paneth N, Casadevall A. 2020. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. medRxiv doi:10.1101/2020.05.12.20099879:2020.05.12.20099879.
84. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, Eubank T, Bernard DW, Eagar TN, Long SW, Subedi S, Olsen RJ, Leveque C, Schwartz MR, Dey M, Chavez-East C, Rogers J, Shehabeldin A, Joseph D, Williams G, Thomas K, Masud F, Talley C, Dlouhy KG, Lopez BV, Hampton C, Lavinder J, Gollihar JD, Maranhao AC, Ippolito GC, Saavedra MO, Cantu CC, Yerramilli P, Pruitt L, Musser JM. 2020. Treatment of COVID-19 Patients with Convalescent Plasma in Houston, Texas. medRxiv doi:10.1101/2020.05.08.20095471:2020.05.08.20095471.
85. Kesici S, Yavuz S, Bayrakci B. 2020. Get rid of the bad first: Therapeutic plasma exchange with convalescent plasma for severe COVID-19. Proceedings of the National Academy of Sciences doi:10.1073/pnas.2006691117:202006691.
86. Anonymous. 2020. Rajeev Venkayya, President, Global Vaccine Business Unit on the latest on the Coronavirus and Takeda. https://www.takeda.com/newsroom/featured-topics/rajeev-venkayya-president-global-vaccine-business-unit-on-the-latest-on-the-coronavirus-and-takeda/. Accessed
87. Anonymous. 2019. Is it time to rethink UK restrictions on blood donation? EClinicalMedicine 15:1-2.
88. Hewitt PE, Ijaz S, Brailsford SR, Brett R, Dicks S, Haywood B, Kennedy IT, Kitchen A, Patel P, Poh J, Russell K, Tettmar KI, Tossell J, Ushiro-Lumb I, Tedder RS. 2014. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet 384:1766-73.
89. Said B, Usdin M, Warburton F, Ijaz S, Tedder RS, Morgan D. 2017. Pork products associated with human infection caused by an emerging phylotype of hepatitis E virus in England and Wales. Epidemiol Infect 145:2417-2423.
90. Tedder RS, Ijaz S, Kitchen A, Ushiro-Lumb I, Tettmar KI, Hewitt P, Andrews N. 2017. Hepatitis E risks: pigs or blood-that is the question. Transfusion 57:267-272.
91. UK. Sep 2017. Guidelines from the expert advisory committee on the Safety of Blood, Tissues and Organs (SaBTO) on measures to protect patients from acquiring hepatitis E virus via transfusion or transplantation. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/680297/Hepatitis_E_Guidelines.pdf.
92. Yilla M, Harcourt BH, Hickman CJ, McGrew M, Tamin A, Goldsmith CS, Bellini WJ, Anderson LJ. 2005. SARS-coronavirus replication in human peripheral monocytes/macrophages. Virus Research 107:93-101.
93. Takada A, Ebihara H, Feldmann H, Geisbert TW, Kawaoka Y. 2007. Epitopes Required for Antibody-Dependent Enhancement of Ebola Virus Infection. The Journal of Infectious Diseases 196:S347-S356.
94. Takada A, Feldmann H, Ksiazek TG, Kawaoka Y. 2003. Antibody-dependent enhancement of Ebola virus infection. J Virol 77:7539-44.
95. Yuan FF, Tanner J, Chan PKS, Biffin S, Dyer WB, Geczy AF, Tang JW, Hui DSC, Sung JJY, Sullivan JS. 2005. Influence of FcγRIIA and MBL polymorphisms on severe acute respiratory syndrome. Tissue Antigens 66:291-296.

96. Zhao J, Yuan Q, Wang H, Liu W, Liao X, Su Y, Wang X, Yuan J, Li T, Li J, Qian S, Hong C, Wang F, Liu Y, Wang Z, He Q, Li Z, He B, Zhang T, Ge S, Liu L, Zhang J, Xia N, Zhang Z. 2020. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. doi:10.1101/2020.03.02.20030189 %J medRxiv:2020.03.02.20030189.
97. Zhang B, Zhou X, Zhu C, Feng F, Qiu Y, Feng J, Jia Q, Song Q, Zhu B, Wang J. 2020. Immune phenotyping based on neutrophil-to-lymphocyte ratio and IgG predicts disease severity and outcome for patients with COVID-19. doi:10.1101/2020.03.12.20035048 %J medRxiv:2020.03.12.20035048.
98. Tan W, Lu Y, Zhang J, Wang J, Dan Y, Tan Z, He X, Qian C, Sun Q, Hu Q, Liu H, Ye S, Xiang X, Zhou Y, Zhang W, Guo Y, Wang X-H, He W, Wan X, Sun F, Wei Q, Chen C, Pan G, Xia J, Mao Q, Chen Y, Deng G. 2020. Viral Kinetics and Antibody Responses in Patients with COVID-19. medRxiv doi:10.1101/2020.03.24.20042382:2020.03.24.20042382.
99. Jiang H-w, Li Y, Zhang H-n, Wang W, Men D, Yang X, Qi H, Zhou J, Tao S-c. 2020. Global profiling of SARS-CoV-2 specific IgG/ IgM responses of convalescents using a proteome microarray. medRxiv doi:10.1101/2020.03.20.20039495:2020.03.20.20039495.
100. Wang X, Guo X, Xin Q, Pan Y, Li J, Chu Y, Feng Y, Wang Q. 2020. Neutralizing Antibodies Responses to SARS-CoV-2 in COVID-19 Inpatients and Convalescent Patients. doi:10.1101/2020.04.15.20065623 %J medRxiv:2020.04.15.20065623.
101. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, Ling Y, Zhang Y, Xun J, Lu L, Jiang S, Lu H, Wen Y, Huang J. 2020. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. doi:10.1101/2020.03.30.20047365 %J medRxiv:2020.03.30.20047365.
102. Zhou W, Wang W, Wang H, Lu R, Tan W. 2013. First infection by all four non-severe acute respiratory syndrome human coronaviruses takes place during childhood. BMC Infect Dis 13:433.
103. Ng K, Faulkner N, Cornish G, Rosa A, Earl C, Wrobel A, Benton D, Roustan C, Bolland W, Thompson R, Agua-Doce A, Hobson P, Heaney J, Rickman H, Paraskevopoulou S, Houlihan CF, Thomson K, Sanchez E, Shin GY, Spyer MJ, Walker PA, Kjaer S, Riddell A, Beale R, Swanton C, Gandhi S, Stockinger B, Gamblin S, McCoy LE, Cherepanov P, Nastouli E, Kassiotis G. 2020. Pre-existing and de novo humoral immunity to SARS-CoV-2 in humans. bioRxiv doi:10.1101/2020.05.14.095414:2020.05.14.095414.
104. Wang S-F, Tseng S-P, Yen C-H, Yang J-Y, Tsao C-H, Shen C-W, Chen K-H, Liu F-T, Liu W-T, Chen Y-MA, Huang JC. 2014. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. Biochemical and Biophysical Research Communications 451:208-214.
105. Lee N, Chan PKS, Ip M, Wong E, Ho J, Ho C, Cockram CS, Hui DS. 2006. Anti-SARS-CoV IgG response in relation to disease severity of severe acute respiratory syndrome. Journal of Clinical Virology 35:179-184.
106. Iwasaki A, Yang Y. 2020. The potential danger of suboptimal antibody responses in COVID-19. Nature Reviews Immunology doi:10.1038/s41577-020-0321-6.
107. Chakraborty S, Edwards K, Buzzanco AS, Memoli MJ, Sherwood R, Mallajosyula V, Xie MM, Gonzalez J, Buffone C, Kathale N, Providenza S, Jagannathan P, Andrews JR, Blish CA, Krammer F, Dugan H, Wilson PC, Pham TD, Boyd SD, Zhang S, Taubenberger JK, Morales T, Schapiro JM, Parsonnet J, Wang TT. 2020. Symptomatic SARS-CoV-2 infections display specific IgG Fc structures. doi:10.1101/2020.05.15.20103341 %J medRxiv:2020.05.15.20103341.
108. Larsen MD, de Graaf EL, Sonneveld ME, Plomp HR, Linty F, Visser R, Brinkhaus M, Sustic T, deTaeye SW, Bentlage AEH, Nouta J, Natunen S, Koeleman CAM, Sainio S, Kootstra NA, Brouwer PJM, Sanders RW, van Gils MJ, de Bruin S, Vlaar APJ, Zaaijer HL, Wuhrer M, van der Schoot CE, Vidarsson G. 2020. Afucosylated immunoglobulin G responses are a hallmark of enveloped virus infections and show an exacerbated phenotype in COVID-19. doi:10.1101/2020.05.18.099507 %J bioRxiv:2020.05.18.099507.
109. Wichmann D, Sperhake JP, Lutgehetmann M, Steurer S, Edler C, Heinemann A, Heinrich F, Mushumba H, Kniep I, Schroder AS, Burdelski C, de Heer G, Nierhaus A, Frings D, Pfefferle S, Becker H, Bredereke-Wiedling H, de Weerth A, Paschen HR, Sheikhzadeh-Eggers S, Stang A, Schmiedel S, Bokemeyer C, Addo MM, Aepfelbacher M, Puschel K, Kluge S. 2020. Autopsy Findings and Venous

Thromboembolism in Patients With COVID-19: A Prospective Cohort Study. Ann Intern Med doi:10.7326/m20-2003.
110. Díez J-M, Romero C, Gajardo R. 2020. Currently available intravenous immunoglobulin (Gamunex©-C and Flebogamma© DIF) contains antibodies reacting against SARS-CoV-2 antigens. bioRxiv doi:10.1101/2020.04.07.029017:2020.04.07.029017.
111. Cao W, Liu X, Bai T, Fan H, Hong K, Song H, Han Y, Lin L, Ruan L, Li T. 2020. High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019. Open Forum Infectious Diseases 7.
112. Cheng Y, Cheng G, Chui CH, Lau FY, Chan PKS, Ng MHL, Sung JJY, Wong RSM. 2005. ABO Blood Group and Susceptibility to Severe Acute Respiratory Syndrome. JAMA 293:1447-1451.
113. Guillon P, Clément M, Sébille V, Rivain J-G, Chou C-F, Ruvoën-Clouet N, Le Pendu J. 2008. Inhibition of the interaction between the SARS-CoV Spike protein and its cellular receptor by anti-histo-blood group antibodies. Glycobiology 18:1085-1093.
114. Neil SJ, McKnight A, Gustafsson K, Weiss RA. 2005. HIV-1 incorporates ABO histo-blood group antigens that sensitize virions to complement-mediated inactivation. Blood 105:4693-9.
115. Han DP, Lohani M, Cho MW. 2007. Specific asparagine-linked glycosylation sites are critical for DC-SIGN- and L-SIGN-mediated severe acute respiratory syndrome coronavirus entry. J Virol 81:12029-39.
116. Kumar S, Maurya VK, Prasad AK, Bhatt MLB, Saxena SK. 2020. Structural, glycosylation and antigenic variation between 2019 novel coronavirus (2019-nCoV) and SARS coronavirus (SARS-CoV). Virusdisease 31:13-21.
117. Zhao J, Yang Y, Huang H, Li D, Gu D, Lu X, Zhang Z, Liu L, Liu T, Liu Y, He Y, Sun B, Wei M, Yang G, Wang X, Zhang L, Zhou X, Xing M, Wang PG. 2020. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. medRxiv doi:10.1101/2020.03.11.20031096:2020.03.11.20031096.
118. Li J, Wang X, Chen J, Cai Y, Deng A, Yang M. 2020. Association between ABO blood groups and risk of SARS-CoV-2 pneumonia. Br J Haematol doi:10.1111/bjh.16797.
119. Zeng X, Fan H, Lu D, Huang F, Meng X, Li Z, Tang M, Zhang J, Liu N, Liu Z, Zhao J, Yin W, An Q, Zhang X, Hu X. 2020. Association between ABO blood groups and clinical outcome of coronavirus disease 2019: Evidence from two cohorts. doi:10.1101/2020.04.15.20063107 %J medRxiv:2020.04.15.20063107.
120. Zietz M, Tatonetti NP. 2020. Testing the association between blood type and COVID-19 infection, intubation, and death. doi:10.1101/2020.04.08.20058073 %J medRxiv:2020.04.08.20058073.
121. Tendulkar AA, Jain PA, Velaye S. 2017. Antibody titers in Group O platelet donors. Asian journal of transfusion science 11:22-27.
122. de França NDG, Poli MCC, Ramos PGdA, Borsoi CSdR, Colella R. 2011. Titers of ABO antibodies in group O blood donors. Revista brasileira de hematologia e hemoterapia 33:259-262.
123. Dai X. 2020. ABO blood group predisposes to COVID-19 severity and cardiovascular diseases. Eur J Prev Cardiol doi:10.1177/2047487320922370:2047487320922370.

Figure 1. Summary of possible convalescent blood products (CBP). Reproduced from reference 110 under STM Permissions Guidelines as of 26 March 2020 (https://www.stm-assoc.org/intellectual-property/permissions/permissions-guidelines/).