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

Focosi Daniele[1, #]

Anderson Arthur O.[2]

Tang Julian W[3]

Tuccori Marco[4, 5]

[1] North-Western Tuscany Blood Bank, Pisa University Hospital, Italy.

[2] Formerly the Chief, Department of Respiratory Mucosal Immunity, US Army Medical Research Institute of Infectious Diseases, Frederick, USA

[3] Respiratory Sciences, University of Leicester, Leicester, UK.

[4] Division of Pharmacology and Pharmacovigilance, Department of Clinical and Experimental Medicine, University of Pisa, Italy.

[5] Unit of Adverse Drug reaction Monitoring, Pisa University Hospital, Italy.

[#] Corresponding author: daniele.focosi@gmail.com . Via Paradisa 2, 56124 Pisa, Italy. Phone/fax : +39 050 996541.

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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 transferring them (8). This approach has been used since 1900 (9) and previous experiences have been reported elsewhere(10). 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 (11). So CBP has been typically administered after early symptoms to maximize efficacy. 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.

Concurrent treatments might synergize or antagonize CP efficacy (e.g. polyclonal intravenous immunoglobulins or steroids) (12).

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 (13, 14), 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 from

plasma across epithelia by the polymeric Ig receptor (pIgR) or by neonatal Fc receptor (FcRn), while IgG can pass into alveolar fluids (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 CBP, with a specific focus on possible applications for COVID-19. 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) (16), 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, have suggested that ELISA ratios/indexes have correlation with PRNT titers : e.g. the Euroimmun ELISA IgG score would detect 60% of samples with titres of >1:100 with 100% specificity using a signal/cutoff reactivity index of 9.1 (17). 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 (18) characterized by reduced S1

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shedding and increased infectivity (19), and more missense mutations accumulating (20). 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(21) and preliminary evidence with COVID19(22) suggest that patients with mild symptoms may develop low-titer antibodies, 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% (23).

A threshold for repeat donations should also be established as soon as banking has reached demand-offer equilibrium (24).

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(25).

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

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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

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)(26) nor the European Center for Disease Control are recommending pathogen reduction technologies (PRT) for CP (27), several national authorities consider that under emergency settings donor screening and conventional NAT viral testing (i.e. HIV, HCV and HBV NAT) would 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 widely 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 (28). Filtration across 75–35 nm hollow fibers could remove large viruses (such as betacoronaviruses) while preserving IgG [48], but has not been implemented yet.

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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 (29) (Theraflex®), amotosalen (S-59) + ultraviolet A (30) (Intercept®), and riboflavin + ultraviolet B (31) (Mirasol®). These methods do not affect immunoglobulin activity.

Fatty acids are also an option. In 2002 it was reported that caprylic acid (32) and octanoic acid (33) were as effective as S/D at inactivating enveloped viruses.

Heat-treatment of plasma has been used in the past (34, 35) but goes with the risk of aggregation of immunoglobulins (36, 37).

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) (38, 39). Such size can be hardly matched from CP donors and facilities rearrangement poses difficult GMP issues (39).

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 (40) and immunoglobulins (6-fold enrichment) (41). The same disposable bag system has also been combined with S/D reduction (28).

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 (42)) is encouraged n order to produce CP asan off-the-shelf, ready-to-use product. Most regulatory system require that CP be 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 by 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 (43). 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(24).

Lessons from SARS

SARS-CoV RNA was found in respiratory specimens from one third of patients for up to 4 weeks following symptoms (44). SARS-specific antibodies usually persist for 2 years(45), and decline in prevalence and titers occurs in the third year (46). Convalescent anti-SARS immunoglobulins were manufactured on a small scale (8, 47). Three infected healthcare workers with SARS progression despite best supportive care survived after transfusion with 500 ml CP: viral load dropped to zero one day after transfusion (48). 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 (49). Amotosalen photochemical inactivation of apheresis platelet concentrates demonstrated a >6.2 log10 mean reduction of SARS-CoV (50). Theraflex˚ reduces infectivity of SARS-CoV in plasma (51). Heating at 60°C for 15-30 minutes

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reduces SARS-CoV from plasma without cells (52), while 60°C for 10 hours is required for plasma products (53). In addition, SARS-CoV was found to be sensitive to S/D (52, 54).

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). Patients with mild disease have very low antibody titers, making CP collection challenging in MERS convalescents (55). 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 (21). CP with a PRNT titre ≥1:80 provide clinical benefit in MERS (56). A case of TRALI following CP transfusion in a patient with MERS was reported (57, 58). MERS-CoV load in plasma was reduced by Theraflex® (59), Intercept® (60), Mirasol® (61), and 56°C heating for 25 minutes (62) : 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, 63), several authors suggested CP as a potential therapeutic agent (64, 65). Of interest, the most critically ill patients show prolonged viremia (strongly correlated with serum IL-6 levels)(10), which makes feasible therapeutic intervention with antivirals and immunoglobulins even in late stages. Viral shedding in survivors can be as long as 37 days (63), mandating SARS-CoV2 RNA screening in CP donors. Serum IgM and IgA antibody appear n COVID-19 as early as 5 days after symptom onset (66), while IgG can be detected at day 14 (67). IgG are generally detected after 20 days (68, 69). Severely ill female patients generate IgG earlier and in higher titers (70, 71): the greatest part of the neutralizing antibody response has been shown to be associated with the IgG_1 and IgG_3 subclasses (72, 73). Duration of anti-SARS-CoV2 antibodies in plasma is currently unknown, though for other betacoronaviruses immunity typically lasts 6-12 months (74). 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. Up to 7 plasma donations have been proven not to decrease antibody titers in convalescent donors(22). In contrast to 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 mildly symptomatic patients suggest low titers(22).

SARS-CoV2 is reduced by > 3.4 logs by Mirasol® (75) (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 (76).

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 (because of risk of developing serum sickness). 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(77).

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 (78).

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 (79).

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 (80). Pei *et al* reported successful treatment of 2 out of 3 patients with 200-500 ml doses of CP (81). Recovery from mechanical ventilation was

also reported by Zhang *et al* in a single patient after CP titrated with anti-N protein ELISA (82). 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 (83). One case recovery in a centenarian patient who received 2 CP units (S-RBD-specific IgG titer >1:640) was also reported(84).

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 (85), while USA centers reported successful treatment with CP in 2 out of 20 cases in a series from Seattle (86), in one case with myelodysplastic syndrome and disseminated tuberculosis (87), a critically ill obstetric patient (in combination with remdesivir) (88), and 2 autologous stem cell transplant recipients (89).

In a single-arm phase II trial (NCT 04321421 (90)) run in Lombardy, 49 moderate-to-severe patients were treated with up to 3 units of PRT-treated CP (250-300 mL/48h) containing neutralizing antibody titers ≥ 1:160 in 96% of cases. Importantly, the viral inoculum was 50 $TCID_{50}$ instead of the usual 100 $TCID_{50}$. Seven-day mortality was 6% vs. 16% in a historical cohort. 1 case of TRALI was reported (91).

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)(92).

Another prospective, multicenter randomized controlled trial from China (ChiCTR2000029757) enrolled 103 severe to life-threatening COVID19 patients. The study was underpowered because of early than expected (200 cases) termination. CP (9-13 ml/kg from donors with S-RBD IgG ≥ 1:640 was associated with negativization of PCR at 72 hours in 87.2% of the CP group vs 37.5% of the BSC group, but clinical improvement at 28 days was statistically different only in severe, but not in life-threatening patients (93).

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 24,000 patients as of June 20, 2020 (https://www.uscovidplasma.org). Preliminary report on the first 20,000 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, expecially if administered before mechanical ventilation (94, 95): donor titers were not disclosed and evidently some donations were not titrated 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) (96).

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 (24).

Several authors have suggested plasma exchange with CP (i.e. high-volume therapeutic plasmapheresis followed by CP transfusion) rather than CP transfusion alone in order to clear proinflammatory cytokines from bloodstream (97), and several successful case reports deploying nonconvalescent plasma have been reported (98-100). One randomized controlled trial (NCT04374539) is ongoing in severe COVID19 patients, but unfortunately no trial to date is testing plasmapheresis followed by CP.

Unfortunately, most trial in Westernized countries (contrary to ones ongoing in China) 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 (eventually of pharmaceutical-grade). 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 using placebo control in late stage patients (refractory to former lines) could pose some ethical concerns because denies treatment opportunities to an unresponsive disease Future trials should investigate combined antiviral and CP therapies.

Notably, several plasma manufacturers are attempting to develop SARS-CoV2-specific hyperimmune sera, (e.g. Takeda's TAK-888 merged with Biotest, BPL, LFB, Octapharma and CSL Behring into the "Convalescent Plasma Coalition" (101); Kedrion and Kamada joint ventures (79)).

Monitoring response to CP 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 (PaO_2/FiO_2 ratio) or radiologically according to target organs. Nevertheless, surrogate endpoints can include anti-SARS-CoV2 antibody titer or absolute lymphocyte count rises in recipient, as well as drops in recipient's SARS-CoV2 viral load or IL-6 levels. 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 (102) – or by some individuals. In addition, there is a now a recognized risk of hepatitis E the within UK blood donor population (103), most

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likely due to the consumption of poorly cooked pork products (104, 105), for which screening has only relatively recently been initiated (71). 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 (106) 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(10)**.**

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 (107, 108), 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 (109)) 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 (70, 110-112), including neutralizing antibodies (113, 114) ; 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 (115, 116)); 3) in SARS, occurrence of ADE has been shown *in vitro* at low antibody titers (117), and in patients high IgG titers and early seroconversion correlate with disease severity(118). Overall, these findings pose concerns on usage of low-titer CP units (119). Another evidence is the high level of

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afucosylated IgG against S protein, facilitating FcR binding, that are produced in the most severely ill patients (120, 121).

A last, COVID-specific concern is worsening of the underlying coagulopathy(122) 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 (123), likely stemming from recent infection with other human betacoronavirus (116). Accordingly, IVIg lead to clinical and radiological recovery in 3 severe Chinese COVID-19 patients(124) and the same team is now leading a randomized controlled trial (NCT04261426).

After demonstration that blood group O healthcare workers were less likely to become infected with SARS-CoV (125), a research group proved that anti-A blood group natural isoagglutinins (which can be also found in CP plasma from blood group O and B donors) inhibit SARS-CoV entry into competent cells (126). Such binding could opsonize virions and induce complement-mediated neutralization (127). Since SARS-CoV2 uses the same receptor as SARS-CoV, anti-A isoagglutinins are expected to have similar effects against SARS-CoV2 (128): accordingly, clusters of glycosylation sites exist proximal to the receptor-binding motif of the S protein from both SARS-CoV (129) and SARS-CoV2 (130). Several publications showed that the odds ratio for acquiring COVID-19 is higher in blood group A than in blood group O (131-135) and one showed that the ABO gene polymorphism to be the most significant at predicting severity of COVID-19(135). COVID-19 has more severe clinical presentations and outcome in elderlies and in males: intriguingly, elderly males are

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known to experience reductions in isoagglutinin titers (136, 137). Although alternative explanations exist(138, 139), studies are hence ongoing to evaluate correlations between isoagglutinin titers and outcome in blood group O and B patients(140). If confirmed, while preserving ABO match compatibility, blood group O and B donors for CP in COVID-19 could be preferred, and their anti-A isoagglutinin titers should be tested.

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
I/II	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
		NCT04397523	Macedonia	20	NA	>5 AU/ml
		NCT04356482	Mexico	90	different amounts of CP	NA

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		NCT04357106	Mexico	10	1 unit of CP (200 ml)	NA
		NCT04384497	Sweden	50	Up to 7 infusions (200 ml each), dose finding study	NA
		NCT04389944	Switzerland	15	2 units of CP (200 ml each)	NA
		NCT04343755	USA	55	NA	> 1:64
		NCT04360486		EAP	NA	NA
		NCT04354831		131	1-2 units of CP (<7 ml/kg adjusted IBW)	NA
		NCT04408040		700	200-425mL CP	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
		NCT04365439	Switzerland	10	NA	NA
		NCT04374565	USA	29	2 units of CP (200 mL each) in 1-2 days	NA
	Severe or critically ill patients	NCT04348877	Egypt	20	1 400 ml unit of CP	NA
		NCT04408209	Greece	60	3 doses of CP	NA

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		NCT04346589	Italy	10	DFPP-collected CP	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; adults: < 450 - 500 ml over 4-6 hours	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
		NCT04343261		15	2 units of CP	NA
		NCT04388527		50	2 units of CP	NA
		NCT04389710		100	1-2 units of CP (200/600 ml)	NA
		NCT04338360		NA	1 unit of CP (200/250 mL)	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		NCT04323800	USA	150 (Exp: 75; Ctr: 75)	1 unit of CP (200-250mL) *vs*. nonconvalescent plasma	>1:64

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	Exposed within 96 hrs of enrollment and 120 hrs of receipt of plasma	NCT04390503		200 (Exp: 100; Ctr: 100)	1 unit of CP (200-250 ml) vs. 5% albumin I.v.	NA
	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* nonconvalescent plasma	NA
		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
		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

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		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
		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
		NCT04397757		80 (Exp: 40; Ctr: NA)	2 units of CP *vs* BSC	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

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		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
		NCT04388410		250 (Exp: 125; Ctr: 125)	2 units of CP vs masked iv saline	NA
		NCT04405310		80 (Exp: 40; Ctr: 40)	1 unit of CP vs. albumin 20%	NA

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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/).

Authors short biographies

Daniele Focosi

Dr. Focosi is a hematologist employed as resident transfusion physician at the largest blood bank in Italy since 2009. He has been transplant immunologist and immunogeticist, quality assurance manager and production manager. He has received awards from the European Federation of Immunogenetics, the European Society of Organ Transplantation, and the Italian Society of Hematology. He has a Ph.D. degree in Clinical and Fundamental Virology, and a master degree in Clinical Trials. He has authored 124 articles indexed in

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PubMed, for a global h-index of 24, on topics ranging from emerging viral infections to new markers of immune compentence .

Arthur Anderson

Dr. Anderson is a Physician/Scientist, Pathologist & Applied Ethicist, Director, Office of Human Use and Ethics & Research Integrity Officer at The US Army Medical Research Institute of Infectious Diseases 1974-2016. He has held faculty appointments The Johns Hopkins University 1972-1974, University of Pennsylvania 1980-1983. An active biomedical researcher for over forty years, Dr. Anderson has close to 100 publications on immunology, infectious diseases and medical research ethics, including one entitled "Ethical Issues in the Development of Drugs and Vaccines for Biodefense." Now, retired from his Civilian Position Dr. Anderson serves as a member of the Board of Trustees at Hood College, Director at Hospice of Frederick County.

Julian Tang

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Prof Tang is a hospital consultant medical virologist, with special interests in the diagnosis, treatment, epidemiology and infection control of influenza and respiratory viruses, congenital viral infections, HIV and blood borne viruses. He also has a PhD in Zoology. He has formerly been associate professor at University of Alberta, and assistant professor at the Chinese University of Hong Kong.

Marco Tuccori

Dr.Tuccori is a clinical pharmacologist with special interest in pharmacovigilance and Pharmacoepidemiology. He has also a PhD in pharmacology and Medical Physiology. He is currently pharmacovigilance manager at the Unit of Adverse Drug Reactions Monitoring of the University Hospital of Pisa and coordinator of the

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Tuscan Regional Centre of Pharmacovigilance. He collaborates with the Agenzia Italiana del Farmaco (AIFA) as member of the Working Group for Signal Detection Analysis on Drugs and Vaccines. He was member of the Advisory Board (formerly Executive Committee) of the International Society of Pharmacovigilance (ISoP) from 2012 to 2019. He is author of about 90 articles in peer reviewed scientific journals and 4 chapters on book.