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COVID-19 convalescent plasma and randomized clinical trials: rebuilding confidence by explaining failures and finding signals of efficacy.

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Abstract

Convalescent plasma (CP) recurs as a frontline treatment in epidemics because it is available as soon as there are survivors. The COVID-19 pandemic represented the first large-scale opportunity to shed light into mechanisms of action, safety and efficacy of convalescent plasma using modern evidence-based medicine approaches. Studies ranging from observational case series to randomized controlled trials (RCT) have reported highly variable efficacy results for COVID-19 CP (CCP), resulting in more doubt than certainty. Reasons for CCP success and failure may be hidden in study details, which are usually difficult to explain to physicians and the public but provide fertile ground for designing next-generation studies. In this paper we analyzed variables associated with efficacy such as clinical settings, disease severity, CCP SARS-CoV-2 antibody levels and function, dose, timing of administration (variously defined as time from onset of symptoms, molecular diagnosis, diagnosis of pneumonia, or hospitalization, or by serostatus), outcomes (defined as hospitalization, requirement for ventilation, clinical improvement or mortality), CCP provenance and time for collection, and criteria for efficacy. Focusing only on the results from the 23 available RCT we noted that these were more likely to show signals of efficacy, including reductions in mortality, if the plasma neutralizing titer was ≥ 160 and the time to randomization was ≤ 9 days, consistent with passive antibody therapy efficacy requiring dosing with sufficient antibody. The fact that most studies revealed signals of efficacy despite variability in CCP and its use suggest robust therapeutic effects that become apparent despite the data noise.

Introduction

In the first 21 years of the 21st century humanity has experienced six major epidemics. The agents involved were SARS-CoV, MERS, influenza A(H_1N_1), Ebola, Zika and SARS-CoV-2 viruses. For five of these outbreaks the response included the use of convalescent plasma (CP) (reviewed in (1, 2)) and it was considered for the sixth (Zika virus). The attraction of CP is that it is readily available as soon as there are convalescing survivors, that unlike drugs or monoclonal antibodies it needs no development, and it is polyclonal, cheap and deployable even in resource poor countries. CP has been proposed as a first line response to new pandemics (3) and was deployed during the COVID-19 pandemic in March 2020 in countries that experienced the early waves of disease such as China (4, 5) and Italy (6).

While in early 2020 most clinical use was reported in case series or small phase II clinical trials (7), beginning in late March 2020 the US expanded access program (EAP) generated a large and robust treatment dataset, with insights on safety and optimal use. This database provided the first clear evidence that CP is safe, which was important given that early in the pandemic there were significant concerns about antibody-dependent enhancement (8). Later, an analysis of the first 3082 patents within the EAP database provided evidence that associated early administration of high titer CCP to non-ventilated hospitalized patients with reduced mortality (9). Before the FDA granted emergency use authorization (EUA), the US EAP provided CCP to as many as 94,287 patients. During the past year, many studies employing either randomized controls (RCT) or propensity score-matched (PSM) controls have been published. RCTs and PSM studies reported so far have had largely opposite outcomes, with most but not all RCTs finding little overall effect on mortality while the PSM and many smaller trials reporting mortality benefits. Several RCTs did not have mortality as a primary endpoint or it was part of a composite endpoint (5, 10-12). These disparate results have led to confusion for both the public and the clinicians, leading to reduced enthusiasm for the use of CP, in part because RCT data is more influential in affecting the opinion of many physicians, specialty societies and government regulators.

As with any other medical treatment, several key factors should be taken into account when evaluating a trial, including the indication (which can be estimated by timing or clinical severity), the therapeutic dose and the intended outcomes. The choices made by the trial designers determine whether the trial will demonstrate or conceal clinical benefit. While much attention is appropriately focused on the performance features of clinical trials (sample size, fidelity to randomization, appropriate analysis), the biological rationale for the hypothesis being tested is critically important but not always taken into account.

Methods

On September 7, 2021, we searched PubMed (which is also indexing the medrXiv prepublishing server) for clinical trials of CCP in COVID19, focusing on RCTs and PSM studies only. Each study was analyzed for the following variables: NCT identifier, recruitment, randomization strategy, type of

control arm, baseline patient status, median neutralizing antibody (nAb) titer in both recipients (before CCP transfusion) and CCP units, type of viral neutralization test (VNT), primary endpoint, signals of efficacy, and reasons for failure

At the same date, the ClinicalTrials.gov database was searched for CCP RCTs worldwide having as status “completed”, “active, not yet recruiting” or “recruiting”.

Results

PubMed search retrieved 23 RCTs and 12 PSM studies about CCP, whose main variables are summarized in Tables 2 and 3. The characteristics of the VNTs used are summarized in Table 1. The variables were reconciled in 4 major topics, discussed in the following sections: the indication, the therapeutic doses, the relevance of CCP to the viral variant, and the intended outcome.

ClinicalTrials.gov search retrieved 8 CCP RCTs completed but not yet prepublished or published, 7 active but not yet recruiting RCTs, and 10 RCTs which are still recruiting (summarized in Table 4).

The indication

While it would be desirable to have a single drug that works at any disease stage, it was not reasonable to expect a silver bullet effect from neutralizing antibody-based treatments such as CCP in later stages of disease. COVID-19 is now well-defined as a disease with two stages, an initial viral phase characterized by flu-like and upper and lower respiratory symptoms, followed, in severe cases, by an inflammatory phase that is characterized by inflammation-driven damage to multiple organ systems, including the lungs that can impair gas exchange and cause life-threatening hypoxia and damage to multiple organs, including the brain and blood vessels (13). Specific intact antibodies in CCP are expected to neutralize SARS-CoV-2 in the intravascular system and, in some patients, prevent progression from early to severe and life-threatening disease (as seen in animal models (14)), but this antiviral therapy cannot be expected to reverse the inflammatory phase of the disease, nor neutralize infectious viruses invading the extravascular system. Thus, COVID-19 is similar to influenza, a disease in which antivirals are effective early in disease but have no effect in later stages when the symptomatology stems largely from the inflammatory response. The rationale for administering CCP as early as possible in the course of COVID-19 stems from the neutralization stoichiometry itself: the larger the number of actively replicating virions in the body, the higher the nAb dose needed for neutralization (15). Some uncontrolled studies have reported a lack of association between early intervention and outcomes (16, 17), but in these studies the level of neutralizing antibody (nAb) or the overall anti-Spike antibody level in the infused CCP was unknown, leaving room for alternative explanations.

At the beginning of the pandemic, some investigators and opinion leaders, riding the wave of CCP successes in anecdotal reports in the media and small case series, introduced CCP to the general public as a panacea for any patient with COVID-19, including life-threatening cases, leading to confusing messaging: after reports of failure in severely ill patients emerged, opinions became polarized and the debate became everything but scientific (18). In clinical trials, the indication (i.e., the

baseline clinical setting) has been variously defined by patient status (outpatient vs. presenting to the emergency room vs. hospitalized vs. ICU-admitted), disease severity (using 5-category COVID-19 Outpatient Ordinal Outcome Scale (19), a 6-category ordinal scale (12), a 7-category COVID-19 severity scale (20), the WHO 8- (21) or 11-category (22) ordinal scales, or pneumological scores such as SOFA), the time elapsed before recruitment (also variably defined as from molecular diagnosis, from onset of hospitalization, from diagnosis of pneumonia, or from onset of symptoms), or by serological status (presence of antibodies or the ability to neutralize SARS-CoV-2). This variability in inclusion criteria for studies has resulted in marked heterogeneity in recruited patients.

An additional complexity in recruitment to CCP trials is time to treatment. Clinical trials involve administrative requirements and consent procedures, and recruitment to a RCT further requires randomization, which may produce delays in treatment. CCP therapy requires matching on blood type, ordering the CCP, which may or may not be available on site, and setting up the transfusion. This inherent delay from randomization to infusion means that RCTs may build in a disadvantage for the CCP study arm, where controls may have received treatment earlier in the disease course (as, for example, in the CP3O trial (23). ABO-compatible CCP units may be not readily available at the local blood bank and recruited patients may have to wait for a compatible unit of CCP. These almost inevitable delays from randomization mean that CCP may be provided later in the illness than is ideal, and even if the trial intends to treat early, in practice it may not be possible.

During a pandemic, moreover, delays in treatment are magnified. The accrual of severely ill patients in emergency departments and the overwhelmed or even collapsed health care systems can create long delays from arrival in the emergency room to treatment. In the absence of quick (antigenic or molecular) tests for SARS-CoV-2, the turnaround time for final confirmation of diagnosis with PCR, which must often be run in batches, can take several hours. All of these factors are likely to impact the efficacy of CCP treatment. To shorten such time, fully screened CCP collected from eligible donors (24) could be safely administered within emergency departments shortly after admission and even before the patient reaches the ward.

The therapeutic dose

Determining the effective dose of CCP is difficult in a pandemic because the antibody assays and other tests needed to assess the potency of any antibody product take time to be developed. In practice, the effective dose is the product of multiple factors, none of which is fully standardized. The first factor is the concentration of the nAbs as measured by a VNT. At the beginning of the pandemic, only a few BSL3 (or higher)-equipped virology laboratories could run VNT using authentic live SARS-CoV-2 virus: the procedure was time-consuming (3-5 days) and the reports were operator-dependent. Nowadays, the availability of Spike-pseudotyped viruses which can be managed under the more widely available BSL-2 laboratories, or cell-free ACE-2 competition assays, combined with automated (e.g., luminescence-based) readings, have standardized outcomes and shortened turnaround times (25): however, harmonization between different assays is still a work in progress (26). The VNT differs according to the type of replication-competent cell line, the viral isolate used for the challenge (which

is critically important when the virus is mutating rapidly as has been the case with emergence of variants of concern), the multiplicity of infection (i.e., the ratio between the viral inoculum - referred with different measuring units – and the number of replication-competent cells within each well), the detection system (optic microscopy for cytopathic effect, immunostaining, quantitative PCR, or luminometer for engineered pseudoviruses), and finally the threshold of neutralization (50% or 90%). The DAWN-plasma RCT provides a clear example of such heterogeneity, with 4 different VNTs used in at different participating laboratories. It was not until August 2020, when many trials were already underway, that the FDA Emergency Use Authorization 26382 defined high-titer CCP on the basis of correlation with a reference standard, the Broad Institute the live-virus, 5-dilution VNT as a 50% inhibitory dilution (ID_{50}) of 1:250 or more (https://www.fda.gov/media/141481/download), and exclusive use of high-titer CCP was formally recommended by the FDA only on March 9, 2021.

Table 1 summarizes the key variables in VNT employed to date in CCP RCTs. Published trials have varied greatly in their approaches to antibody quantification whether in measured transfused CCP units or in recipients. Many trials have relied on high-throughput semi-quantitative or qualitative assays with a poor-to-moderate relationship with nAb titers. Although most trials performed a correlation analysis between VNT and high-throughput serological assays, in many cases the CCP units were tested only with the latter without validation, as was the case with 66% of the patients in the PlasmAR trial (12). This procedure risks an incorrect evaluation of the neutralizing CCP activity. Another cause for discrepancies in outcomes could be that although IgM, IgG, and IgA are all capable of mediating neutralization, VNT titers correlate better with binding levels of IgM and IgA_1 than they do with IgG (27). Yet it is IgG that is routinely measured in high-throughput serological assays, and these assays include non-neutralizing IgGs, the role of which in activity against SARS-CoV-2 has not been established. Trials should preferentially use VNTs to assess serostatus of transfused units and not rely on high-throughput serology.

As for any other medicinal product, CCP exhibits a dose-response relationship, which is also evident when using high-throughput assays. In the subgroup analysis of the EAP, a gradient of mortality was seen in relation to IgG antibody levels in the transfused CCP. In the subgroup of patients who were not receiving mechanical ventilation, death within 30 days after CCP transfusion occurred in 81 of 365 patients (22.2%; 95% CI, 18.2 to 26.7) in the low titer group, 251 of 1297 patients (19.4%; 95% CI, 17.3 to 21.6) in the medium-titer group, and 50 of 352 patients (14.2%; 95% CI, 10.9 to 18.2) in the high-titer group. Depending on the statistical model, the RR for 30-day mortality in high-titer CCP compared to low-titer CCP recipients ranged from 0.64 – 0.67, with an upper 95% confidence bound of 0.91 (8). Similarly, the large retrospective PSM study from HCA reported a 0.2% decreased risk of mortality for every 1 unit of S/Co serology level (28).

The nAb titer (or total IgG levels as measured by surrogate assays) only describes one factor involved in defining the real therapeutic dose in that it represents the concentration of just one (likely the main) active ingredient. But CCP contains additional antibodies that mediate antibody-dependent cellular cytotoxicity (ADCC), complement activation and phagocytosis of viral particles, functions that can each contribute to its antiviral effects (29). At this time the relative importance of nAbs vs. the other

antibody activities is not understood, but, hopefully, retrospective analyses that correlate CCP efficacy with these activities will reveal additional variables that need to be considered in choosing optimal CCP units.

Despite these uncertainties, we can make estimates of likely effective doses based on the available clinical experience thus far. The therapeutic dose of nAb is a product of its concentration in the infused CP multiplied by the overall infused CP volume, adjusted to the recipient body weight to take account of dilution into the blood volume and tissues. RCTs have varied in the provision of volume per unit (200-300 ml), and most importantly in cumulative volume per patient (1-4 units) and in extent of exposure to diverse antibodies from various CCP donors, and no published trials have adjusted levels of nAbs by recipient body weight (or, when attempts have been performed, they referred to the old-fashioned 10-15 ml/kg dose inferred from treatment of hemorrhagic coagulopathies (30)). A failure of CCP to improve outcomes when 200-ml of 1:160 nAb-titer CCP is provided to a patient who weighs 120 kg represents quite a different scenario from failure of a 600-ml transfusion of 1:640 nAb-titer CCP to produce improvement in a 60-kg patient. But these central issues in dosage have not been considered in the RCTs published so far.

Several RCTs performed nAb titration, but with highly heterogenous methods which makes comparability of doses across studies difficult. Table 1 attempts to reconcile doses across those trials, showing that they actually differed more than was apparent by inspection of raw titers. The lack of utility from low-titer (1:40) CCP in moderate COVID-19 was confirmed by the PLACID trial (10). As long as a clear therapeutic dose is not identified, it seems prudent to transfuse units containing nAb titers at least 10-fold higher than the nAb titer measured before transfusion in recipient serum. Similarly, the ConCOVID RCT showed that CCP units having nAb titers similar to those of the recipients (1:160) did not confer a clinical benefit (31). CCP units with an adequate nAb titer (nowadays estimated at $\geq$1:160) are more easily found among older males who recovered from a previous symptomatic COVID-19 requiring hospitalization (32, 33): unfortunately, such donors were poorly represented in the first donation waves, which tended to obtain CCP from younger donors will mild disease, and, presumably lower nAb titers (10).

Relevance of CCP to the viral variant

Albeit not formally demonstrated, CCP manufactured by pooling ABO-matched transfusion from many different donors (e.g., in PlasmAr (12)) theoretically have greater polyclonality of nAbs than repeated CCP doses from a single-donor (e.g. CAPSID (34)) and should grant higher efficacy against viral variants. Nevertheless, pooling typically occurs among donors attending the same blood bank, making donor exposure to different viral variants unlikely.

An analysis of potential variables associated with CCP efficacy associated near-sourcing with reduced mortality, with the efficacy of CCP in reducing mortality falling sharply when the CCP source was more than 150 miles from where it was used (35). This finding suggests that SARS-CoV-2 viruses vary enough in their antigenic composition in different geographic locations to create antibody

responses that differ by locale (36). Even though CCP is often standardized for nAb titer to the Spike protein, the VNT could use a nonrelevant viral strain, or miss major functional differences for the antibody response (29). This finding has implication for RCTs that use nationally sourced (centralized) CCP, since the attempt to standardize the therapeutic units centrally could inadvertently reduce CCP efficacy if hospitals use CCP obtained from distant loci. For example, in the C3PO RCT, which was conducted in 21 USA states, 95% of the donor CCP was collected in either Chicago or Denver: since only 4 of the 48 centers were in Illinois or Colorado, most CCP usage had to be from remote sources (23). By contrast, the NCT04359810 RCT in New York and Brazil used CCP locally sourced in New York, whose efficacy against P.1 was tested to ensure efficacy at the other recruiting center in Brazil (11).

Although also not formally demonstrated during clinical trials, it is also reasonable to assume that CCP collected during early pandemic waves could be less effective against currently circulating variants of concern (37). RCTs whose recruitment was protracted across multiple pandemic waves (e.g., ConPlas-19) and which relied on CCP collected and banked months earlier could have inadvertently used CCP with reduced activity against the SARS-CoV-2 strains circulating the community when the therapy was administered. Hence, both geography and time of collection of the CCP are important variables when considering the efficacy of the treatment.

The intended outcomes

Most trials (CONTAIN, COMPILE, and PassItOn being exceptions) have used composite endpoints or specialty scores (e.g., SOFA) rather than progression in the simple WHO ordinal scale or mortality, and many were stopped because of apparent futility at a time when they may have been underpowered to detect significant benefit. As represented in Figure 1, several studies have reported overall negative results (panel A) despite the presence of positive signals of efficacy just barely missing statistical significance (panels B and C). The significance level (i.e., p= 0.05) is largely a socially constructed convention for rejecting the null hypotheses, but it has often been misinterpreted as a measure of reality by many individuals not familiar with the nuances of statistics. For example, some CCP studies have concluded that a difference that did not achieve a p value < 0.05 was an absence of difference, even when mortality in the CCP arm was ~20-40% lower than in controls. This reasoning played a central role in the polarized views of CCP efficacy and prevented subsequent studies to drill down on positive effects that were observed. The dogged pursuit of statistical significance, viewed as a measure of reality instead of the actual reality demonstrated by the data, during a public health emergency dealt a serious blow to studies of CCP and created significant confusion for clinicians. It is also important to understand that RCTs are powered to be less tolerant of Type I error than Type II error, which are conventionally set at .05 and .20, meaning that a Type II error is expected four times as often as a Type 1 error. This statistical convention can contribute to the absence of significance in studies that were set up early in the pandemic when there was little information on expected effects for the various patient populations studied and the patients were very heterogenous such that only subgroups may have responded. Many studies were originally designed

to enroll patients at any disease stage, and it should be no surprise that subgroup analyses on the groups that were later demonstrated more likely to benefit from CCP (e.g., early treated, seronegative patients, those receiving high nAb titre) were underpowered to reach statistical significance, as shown by orange color predominance in panel C of Figure 2. Nevertheless, favorable trends are a shared feature across such trials. Lastly, rigid adherence to primary outcomes that were often fixed in the early days of the pandemic when information about disease stage and quality of CCP associated with efficacy were not understood. When these outcomes were not met, trials were considered failures even though there were often signals of efficacy in the data that were not considered as valuable since these had not been pre-specified, even when they made biological sense. For example, in the New York-Brazil RCT cited above, CCP did not lower the primary end-point of clinical status on an ordinal scale, but the statistically significant halving of mortality was acknowledged in the abstract. Would it have made sense to ignore the strong effect of CCP on mortality in this trial just because mortality was not selected as a primary outcome? Although we agree that subgroup analysis carries the risk of 'cherry picking' data, such analyses are often important for hypothesis generation and critically important during the emergency of a pandemic where neither viral pathogenesis nor therapeutic variables are well understood. When sub-group analyses are based on firm biological principles, such as focusing on those treated early in disease or lacking their own serological response, the exercise is not cherry picking. To emphasize this point, Christopher Columbus missed the pre-specified primary endpoint of his mission - reaching India - but no one considers his discovery of the New World to be a failure! Turning to the clinical arena, most trials of anticoagulants in myocardial infarction found reductions in mortality of about 20-25%, which was generally not significant in these underpowered trials that declared the findings to be null, even though such a mortality reduction would clearly be of value (38).

Another misunderstood endpoint is viral clearance, defined as the conversion of nasopharyngeal swabs (NPS) from positive to negative for PCR evidence of SARS-CoV-2 in CCP-treated patients. While there was early and robust evidence for this effect from CCP (4, 10), some RCTs failed to find differences between arms just because they sampled NPS too late after CCP treatment, when the endogenous immune response had also mounted in the control arm, and differences vanished.

Analyzing failures in individual RCTs.

We use the word 'failures' with care and considerable nuance, since negative trials can be very important in teaching us about populations that do not benefit from CCP or variables that affect its efficacy. Keeping the factors discussed above in mind, we have analyzed individual RCTs in detail. At the very beginning, many historically or internally controlled observational studies showed clinical benefit from CCP and this led the FDA to issue an EAP in March 2020 that was converted into an emergency use authorization (EUA) in August 23, 2020. The largest observational study is the US open-label EAP (NCT04338360) led from Joyner *et al*, which enrolled 105,717 hospitalized patients with severe or life-threatening COVID-19 from April 3 to August 23, 2020 (39). In an analysis of the

effect of antibody in CCP performed independently of the results cited above (8) and using a nAb titer in an overlapping but non-identical group of EAP patients, the FDA showed that the 7-day mortality in non-intubated patients who were younger than 80 years of age and were treated within 72 hours after diagnosis was 6.3% in those receiving high-titer CCP and 11.3% in those receiving low-titer CCP (https://www.fda.gov/media/142386/download).

In a later analysis of a larger (N = 35,322) subset of EAP patients, (including 52.3% in the intensive care unit (ICU) and 27.5% receiving mechanical ventilation), the 7-day mortality rate was 8.7% in patients transfused within 3 days of diagnosis but 11.9% in patients transfused ≥4 days after diagnosis. Similar findings again from the US EAP were observed in 30-day mortality (21.6% vs. 26.7%) (40). The major criticism of these results is that controls were neither randomized nor PSM: hence a difference in the treatment outcome between treated and untreated groups may be caused by a factor that predicts treatment rather than by the treatment itself. However, importantly, nAb titer analysis was retrospectively done, both patients and physicians were unaware of the nAb content in the CCP units used, the results are what would have been expected from the experience with antibody therapy, and multivariate models were used to adjust for potential confounders (1). Additionally, given the outline of an optimal use case with this data and the earlier underpowered RCT by Li *et al* (5), it is unfortunate that due to (a) lack of awareness and (b) logistical burden associated with protocol adjustments, involving repowering and new patients' recruitment criteria, later treatment RCTs either continued or initiated without modifications to include newly available evidence.

The highest level of scientific evidence in primary clinical research stems from prospective PSM and RCTs. PSM studies (Table 3) balance treatment and control groups on a large number of covariates without losing a large number of observations. Unfortunately, no PSM study to date has investigated nAb titers by VNT, and all times have been reported since hospitalization (excluding outpatients). Nevertheless, in 2 retrospective PSM studies from 2 different hospitals in New York, trends for improved outcomes in non-intubated and those treated within 7 days since hospitalization (HR 0.33) were observed (41, 42). These findings were later confirmed in a prospective PSM study from Houston (43, 44). Of interest, a retrospective PSM study from Providence did not show any benefit, but patients were treated at a median of 7 days after onset of symptoms (45). Another PSM study from Yale associated CCP with a 35% reduction in mortality (46). That study is notable in that it included patients on mechanical ventilation who would not normally be expected to benefit from CCP and the percentage of individuals receiving corticosteroids was very low since the study was conducted in the early days of the pandemic in the USA. Another PSM from the Washington DC area found a reduction in mortality with CCP use at both days 14 and 28, which reached statistical significance at the earlier date (47). Finally, a very large study from 176 community hospitals affiliated with Healthcare Corporation of America confirmed substantial mortality reduction in hospitalized patients receiving CCP within 3 days from admission (48).

Since PSM only accounts for observed (and observable) covariates, and not latent characteristics, RCT remains the gold standard for highest-level evidence (Table 2). In the PlasmAr RCT, the small number of early arrivals (less than 72 hours) showed superior primary and secondary outcomes in the

CCP arm (n= 28) compared to the placebo arm (n=11), but the minimal contribution of this group to the overall cohort (228 CCP and 105 placebo) made the advantage disappear in the final outcomes at day 30 (12). In another Argentinean RCT on 160 outpatients older than 65 years of age with mild COVID-19 who were treated with CCP within 72 hours, progression to severe COVID-19 halved at day 30 (49). An RCT from India reported that patients younger than 67 treated at a median of 4 days after hospital admission manifested superior mitigation of hypoxia and survival in the CCP arm (50). Another RCT in Spain enrolling patients at less than 7 days of hospitalization showed four deaths in the control arm, none in the CCP arm (51). Given that conventional peer-review slows down during a pandemic, pre-publishing RCT results by the preprint mechanism should be encouraged to accelerate sharing of potentially life-saving therapeutic approaches and to provide pre-publication review that could improve the quality of the final published study.

Figure 1 graphically places the outcomes of RCTs and PSM studies on a Cartesian plot having timeliness and nAbs dose as variables (if values are disclosed in the reports): this makes immediately clear that the few successes at reaching the primary endpoints have gathered into the lower right corner (high nAb dose and early intervention), while the many “failures” have been scattered all around (panel A), reflecting lower antibody levels infused or late treatment, or both, with the latter being the commoner problem. Nevertheless, when we focus on mortality irrespective of statistical significance (panel B) or focusing on statistical significance (panel C), many more RCTs showed clear benefits.

We will focus here on “failures” as identified by title, abstract and/or press recognition. Narratively, we could group so-called “failures”, with failure implying inability to demonstrate a favorable outcome to CCP use, into 4 categories, according to the main reasons:

1. Trials that transfused insufficient therapeutic doses of CCP due to either low total IgG levels or low nAb levels (e.g., PLACID)
2. Trials that transfused appropriate doses of CCP but too late, but which nevertheless reported signals of efficacy (e.g., RECOVERY, CAPSID, NCT04359810 and TSUNAMI)
3. Trials that were stopped too early to observe benefit or with inherent design flaws, and/or were underpowered such that likelihood of success was reduced (e.g., C3PO)
4. Trial in which CCP was used to treat a condition not amenable to antibody intervention, such as hypoxia that is caused by pulmonary inflammation

Stopping trials for futility is an occurrence that deserves special attention, because it represents wasted resources during a pandemic. Six RCTs so far have been halted for futility, namely RECOVERY, REMAP-CAP, CONCOR-1, C3PO, and NCT04361253, with the first one being to date the strongest evidence for futility (30), with its massive recruitment affecting the outcomes of systematic reviews (52). Instead of stopping trials for futility based on pre-set endpoints it makes more sense that DSMBs facing a high likelihood of lack of statistical significance provide advice on trial modifications that are likely to amplify the significance of signals of efficacy evident in these studies. This would seem a more responsible action than trial cessation given the paucity of therapeutic

alternatives in the pandemic emergency. Indeed, a Bayesian re-analysis of RECOVERY data with a wide variety of priors (vague, optimistic, skeptical and pessimistic) calculated the posterior probability for both any benefit or a modest benefit (number needed to treat of 100). Across all patients, when analyzed with a vague prior, the likelihood of any benefit or a modest benefit was estimated to be 64% and 18% respectively. In contrast, in the seronegative subgroup, the likelihood of any benefit or a modest benefit was estimated to be 90% and 74% (53). This finding of benefit accruing to specific sub-groups, who were not determined post-hoc but because they were likely to benefit based on understanding of principles of CP treatment is found in nearly every trial whose overall finding is negative.

The inadequacy of meta-analyses.

With all the heterogeneity in key drivers discussed in the former paragraphs, it becomes clear that secondary research (ranging from umbrella reviews to meta-analyses to systematic reviews), whereby each study is considered at the same level, invariably ends up with biased and divergent conclusions. This adds confusion to the already complex field of individual trial outcomes. Amazingly, as of August 24, 2021, PubMed has indexed 25 meta-analyses on CCP efficacy, more than the RCTs reported at the same date. Until the beginning of 2021, meta-analyses (variably including observational studies) were generally in favor of CCP (54), but began to be biased towards failure after publication of the large RECOVERY trial (30), which, by enrolling as many as 11,448 patients, diluted all the other divergent RCTs. Clear examples of this phenomenon come from a widely cited metanalysis from Janiaud *et al* in *JAMA* (52) which included press release data from RECOVERY and from the living systematic review by the Cochrane Group (55). This paper was surely unprecedented in the tradition of meta-analysis, not only because it included a study based only on a news release (which proved to differ in some important respects from the published paper), but because it allowed these data from a news release to dominate the entire analysis. Several groups attempted to dissect the RECOVERY trial and others by running subgroup analyses in their systematic reviews (53, 56, 57), but these reviews were unable to restore confidence in CCP efficacy in the clinical community that had been lost because of the publication of the overall negative findings of RECOVERY and PlasmAr (58). A metanalysis of 22,591 patients (enrolled in 10 RCTs and 15 observational studies) showed that early CCP significantly reduced mortality (RR 0.72, $p<0.00001$), but only in patients who were not suffering severe or critical disease (59). On the other hand, another metanalysis of 18 peer-review clinical trials, 3 preprints, and 26 observational studies actually found that CCP use was associated with reduced risk of all-cause mortality in severe or critical COVID-19 patients (60). A recent umbrella review of 29 metanalyses and systematic reviews found evidences for improvement in the CCP arms for some outcomes (overall mortality, viral clearance at day 3,) but not for others (clinical improvement, length of hospital stay (61).

Rather than pooling published RCTs, the Continuous Monitoring of Pooled International Trials of Convalescent Plasma for COVID-19 Hospitalized Patients (COMPILE) study pooled individual patient

data from ongoing RCTs at two-week intervals. Unfortunately, with the single exception of CONTAIN, participating RCTs largely shared late usage (DAWN-plasma, PLACID, ConCOVID, ConPlas-19, NCT04421404, NCT04397757, and the Brasília Covid-19 Convalescent Plasma (BCCP)) (62).

Conclusions

While CCP contains a plethora of biologically active molecules (63), we now have very strong evidence that appropriately vetted CCP from eligible convalescent donors is safe for patients (64, 65), with no evidence of increased risks of transfusion-transmitted acute lung injury, antibody-mediated enhancement concerns feared in the early days of the pandemic (66) nor is there evidence that CCP induces accelerated SARS-CoV-2 evolution (11). Polyclonal antibodies such as CCP, or CCP-derived hyperimmune globulins made from large donor pools, are likely to offer better protection against onset of variants than monoclonal antibodies. Outcomes in immunocompromised patients treated with CCP have been successful in the long-term, with minimal evidence for immune escape (67). There is evidence that vaccinated convalescents may have even higher nAb titers than unvaccinated convalescents offering the promise of expanded success in using CCP (68).

We have also learned that CCP is less likely to benefit patients requiring oxygen (i.e., from level 4 and up on the 11-point WHO ordinal scale), and hence, ideally, the focus should be on outpatients and in identifying that subset of patients who seek hospital care and are still sufficiently early in the course of disease such that they can benefit from CCP. This finding parallels the finding with hyperimmune serum and anti-Spike monoclonal antibodies, which at first failed in hospitalized patients (69, 70), but later succeeded for ambulatory patients with mild to moderate COVID-19 (71) and were approved for emergency use. However, at this moment clinical use in the US is restricted by the FDA to inpatients.

CCP usage per admission peaked after issuance of the EUA, with more than 40% of inpatients estimated to have received CCP between late September and early November 2020. However, following reports of RCTs that failed to show clear benefit from CCP, usage per admissions declined steadily to a nadir of less than 10% in March 2021. A strong inverse correlation (Pearson correlation coefficient of -0.5176 with P = 0.00242) was found between CCP usage/hospital admission and deaths occurring 2 weeks after admission, and this finding was robust to examination of deaths taking place 1, 2 or 3 weeks after admission. Changes in the number of hospital admissions, prevalence of variants, and age of patients could not explain these findings. The authors estimated that the retreat from CCP usage, a phenomenon they termed “plasma hesitancy”, might have resulted in 29,000 to 36,000 excess deaths in the period from mid-November 2020 to February 2021 (72). The same analysis estimated that USA had avoided 96,000 excess deaths from August 2020 to March 2021 by its liberal deployment of CCP.

Several lines of evidence, ranging from the EAP to clinical trials employing RCT or PSM controls are now indicating how CCP should be used in immunocompetent patients (73). The evidence supports the initiation of CCP treatment as early as 44-72 hours within onset of symptoms (which largely pertains to outpatients) and using CCP with a nAb titer > 1:160. Benefit within 1 week from onset of symptoms (including in hospitalized patients) is less well understood, although a benefit from higher

therapeutic doses cannot be ruled out at this stage. Clinical benefit seems absent when administered after 1 week from onset of symptoms or in patients requiring ventilation, or in those who receive CCP with a low nAb titer. Nevertheless, chronically immunosuppressed patients benefit from CCP even at later stages (67, 74, 75) : the best evidence for this scenario comes from a prospective PSM showing a halving of mortality in ICU-admitted oncohematological COVID-19 patients who received CCP (76). We note that while there have been concerns that use in immuncompromised can promote the emergence of antibody-resistant variants, such variants have emerged from massive replication in susceptible populations and not from treated patients, who in any case are isolated in hospitals where mitigation efforts to reduce transmission are employed, and are thus very unlikely to transmit their viruses further (77). Such simple concepts have been poorly communicated to the general public and the clinical community, who should be better informed of the state of current evidence that support CCP efficacy.

The future of CCP

CCP remains a relatively inexpensive therapy that is available throughout the world even in resource poor areas that cannot afford expensive antiviral drugs or monoclonal antibody therapies. Much has been learned about the variables that affect CCP efficacy even though, as recounted here, the clinical efficacy data is mixed. Table 4 lists the RCTs whose outcomes have still to be reported after completion or which are still recruiting patients. Unfortunately, little new can be expected given that most of these RCTs were designed to enroll patients having symptoms for more than 7 days. Given the heterogeneity of the product and the complex variables that contribute to efficacy it is remarkable that many studies have reported reductions in mortality. This suggests a robust therapeutic effect that allow signals of efficacy to break through all the noise imposed by variability in the product and its clinical use. The positive evidence for CCP efficacy cannot be dismissed while negative results can be explained. In the absence of good therapeutic options for COVID-19, CCP is likely to find a niche in the early treatment of disease. Instead of looking for unlikely superiority outcomes, noninferiority RCTs comparing monoclonal antibody versus CCP in early arrivals should be initiated. Such an RCT is very unlikely to be sponsored by vendor companies, so public institutions should be sensitized to funding it.

Given the experience accumulated with COVID-19, it is almost certain that CP will again be deployed for the next epidemic and we are hopeful that lessons learned in this pandemic are heeded such that use and trials focus on the very early use with high-titer CP.

We declare we have no conflict of interest to disclose.

Figure 1

Simplified graphical representation of CCP RCTs reported to date, plotted according to earliness of intervention and nAb titers in CCP. In **panel A**, green text indicates trials which met the primary endpoint with statistical significance; orange text indicates trials which failed to meet the primary endpoint but showed statistically nonsignificant trends in favor of CCP; red text indicates trials which failed to show and benefit from CCP in the primary endpoint. In **panel B**, green text indicates trials which showed overall mortality benefit from CCP; orange text indicates trials which showed mortality benefit from CCP in the subgroup of early arrivals or higher nAb titers; red text indicates trials which failed to show any mortality benefit from CCP. In **panel C**, green text indicates trials which showed statistically significant mortality benefit from CCP (overall or in the subgroup of early arrivals or higher nAb titers); orange text indicates trials which showed statistical trends towards mortality benefit from CCP (overall or in the subgroup of early arrivals); red text indicates trials which failed to show any mortality benefit trend from CCP in any subgroup. Underlined text indicates large trials which were not RCT and for which nAb levels was inferred from high-throughput serology, but are nevertheless reported as reference studies. Numbers in parenthesis indicate cumulative number of patients enrolled.

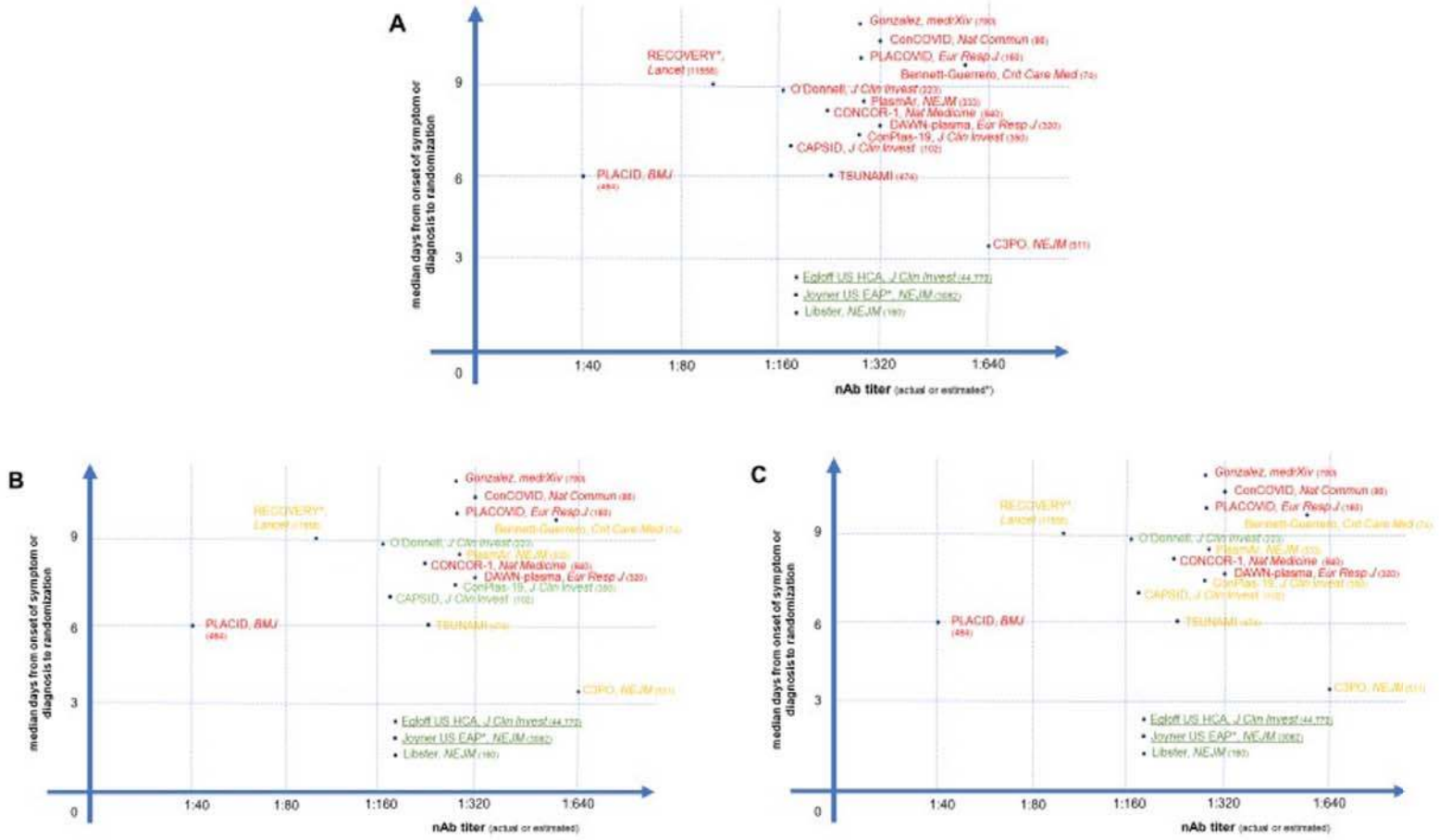

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Table 1

Details of viral neutralization tests (VNT) employed in CCP RCTs. Information was retrieved from original article (including Supplementary Appendix). Whenever not reported, the corresponding author was contacted (marked with *). If the details could not be retrieved the field is labelled "n.a." (not available). IC: inhibitory concentration. NT: neutralization titer. PFU: plaque-forming unit.

	RCT (acronym/first author)	cell line	cells seeded per well	virus lineage	virus per well	multiplicity of infection (MOI)	length of incubation	assay read-out	threshold	protocol reference
authentic live SARS-CoV-2	NeuCoV-NET NCT04393727 (TSUNAMI)	Vero E6	12,000	SARS-CoV-2/Human/ITA/PAVIA10734/2020 (D614G)	100 $TCID_{50}$	0.01	until the cytopathic effect (CPE) became evident.	CPE	last serum dilution that inhibited SARS-CoV-2 CPE by 90%.	(78)
	NCT04433910 (CAPSID)	Vero E6	n.a.	n.a.	100 PFU	n.a.	3 days	CPE	$PRNT_{50}$	(79)
	Broad Institute on a high throughput platform (BROAD PRNT). Part of NCT04355767 (C3PO)	Vero E6-TMPRSS2	10,000	SARS-CoV-2 live virus (D614)	n.a.	n.a.	48 hours	N-protein ELISA	samples whose curves lay above 0.5 for all the data points were considered non-neutralizing, with ID_{50}=20, while samples whose curves fell below 0.5 were considered highly neutralizing and assigned an ID_{50}=10,240.	(80)
	NCT04359810 (O'Donnell)	Vero E6	10,000	2019-nCoV/USA-WA1-2020	100 $TCID_{50}$	0.01	48 hours	Triplex CII-SARS-CoV-2 rRT-PCR Test, EUA200510).	the highest CCP dilution that prevented virus growth (cycle threshold [Ct] was rated as neutralization titer.	(11)

	NCT04348656 (CONCOR-1)	Vero-E6	n.a.	Canada/ON_ON-VIDO-01-2/2020, EPI_ISL_42517	50 PFU	n.a.	72 hours	CPE	$PRNT_{50}$	(81)
	NCT04342182 (ConCOVID)	Vero-E6	n.a.	German isolate (GISAID ID EPI_ISL 406862)	400 PFU	n.a.	8 hours	CTL ImmunoSpot Image Analyzer	reciprocal of the highest dilution resulting in a reduction >50% of infected cells ($PRNT_{50}$)	(31)
	NCT04429854 (DAWN-plasma)	Vero E6	n.a.	BetaCov/Belgium/Sart-Tilman/2020/1	100 $TCID_{50}$	n.a.	5 days	CPE	$PRNT_{50}$	(82)
			18,000	2019-nCoV-Italy-INMI1	3 $TCID_{50}$	n.a.				(83)
			n.a.	Belgium/GHB-03021/2020	400 PFU	n.a.	4 days			(84)
			20,000	Belgium/S1871/2020	100 $TCID_{50}$	n.a.	2 days	anti-N staining	NT_{50}	(85, 86)
Spike pseudotyped viruses	Vitalant Research Institute (VRI) Pseudovirus Neutralization Part of NCT04355767 (C3PO)	ACE2 and TMPRSS2 expressing HEK293T cells	n.a.	VSV pseudotyped with Wuhan-Hu-1 Spike (D614G mutation and without 21 C-	n.a.	n.a.	18-24 hours	chemiluminescence reader	NT were calculated as a percentage of no-serum control and the NT_{50} was estimated from the dilution curve	(80)

				terminal aa)						
	NCT04383535 (PlasmAr)	Vero-CCL81	20,000	VSV pseudotyped with Spike (CoV2pp) and carrying *Renilla* luciferase gene in place of its G glycoprotein (VSVΔG-rLuc).	n.a.	n.a.	18-22 hours	luminometer	IC_{50} is calculated as the midway point between the upper and lower plateaus of the curve. absIC_{80} appeared to be a more stringent measure of nAb activity, as some sera that have respectable MN absIC_{50} titers never achieve an absIC_{80}; this is due in part to the difference in the dynamic ranges between a luciferase-based assay (≥3 logs RLUs) and a MN assay (~1.5-log optical density [OD] values corresponding to the amount of viral protein detected).	(87)
	CTRI/2020/04/024775 (PLACID)	Vero CCL-81 293 T/ACE2 cells	10,000	SARS-CoV-2 strain NIV2020770	n.a.	n.a.	36 hours	luminometer	n.a.	(88)
	NCT04345523 (ConPlas-19)	Vero E6	5,000	lentivirus pseudotyped with Spike and luciferase	titrated at 10 ng p24 Gag	n.a.	48 hours	luminometer	ID_{50} expressed as the highest dilution of plasma (reciprocal dilution), which resulted in a 50% reduction of luciferase activity compared to control without serum. Sigmoid curves were generated and ID_{50} neutralization titers (NT_{50}) were calculated by non-linear regression	(20)

	NCT04375098 (Elvira-Balcells)	HEK293T/hACE2	10,000*	HIV-1–SΔ19 pseudotyped with Spike (Genebank: QHU36824.1) and luciferase	n.a.	n.a.	48 hours*	luminometer	samples with a neutralizing activity of at least 50% at a 1:160 dilution were considered positive and used to perform titration curves and ID_{50} NT calculations	(89)
	NCT04344535 (Bennett-Guerrero)	n.a.	n.a.	PRNT and pseudovirus	n.a.	n.a.	n.a.	n.a.	n.a.	(90)

Table 2

Randomized controlled trials (RCT) of COVID-19 convalescent plasma (CCP) reported to date. nAb: neutralizing antibodies. BSC: best supportive care. FFP: fresh frozen (nonconvalescent) plasma. n.a.: not assessed (i.e. antivirus antibodies were assessed only using high-throughput serology). IQR: interquartile range.

RCT identifier (acronym/ first author)	recruitment (out of expected) (randomization strategy)	control arm	median days before randomization	baseline recipient 8-point WHO score* (21)	transfused CCP volume (ml)	median nAb titer in CCP units	median pretransfusion nAb titer in recipient	main outcomes reported in abstract or conclusions	likely reason(s) for failure	signals of efficacy	ref
NCT04479163 (Libster)	160 (out of 210) (1:1)	normal saline	39.6 hours (from symptoms; and > 65 yrs)	2	250	n.a.	n.a.	progression to severe COVID-19 halved at day 30	no failure	-	(49)
BKH-CT-012	49 (1:1)	BSC	< 3 (from RCU admission)	5	400	n.a.	n.a.	duration of infection reduced by 4 days; mortality 1/21 in CCP arm vs 8/28	no failure	-	(91)
CTRI/2020/05/025209 (Raj)	80 (1:1)	BSC	4.2 (from hospital admission)	5	200+200	n.a.	n.a.	immediate mitigation of hypoxia, reduction in hospital stay as well as survival benefit was recorded in severe COVID-19 patients with ARDS aged less than 67 years	no failure	-	(50)

ChiCTR2000029757 (Li)	103 (out of 200) (1:1)	BSC	30 (from symptoms)	5-6	200	n.a.	n.a.	no significant difference in 28-day mortality (15.7% vs 24.0%) or time from randomization to day-28 discharge (51.0% vs 36.0%)	moderately late usage	reduced mortality at day 28 only in WHO score 5 patients (HR 2.5); negative conversion rate of viral PCR at 72 hours in 87.2% of the CCP group vs 37.5% of the control group (OR, 11.39)	(5)
NCT04342182 (ConCOVID)	86 (out of 426) (1:1)	BSC	10 from symptoms; 2 from hospitalization	5-6	300	1:320 ($PRNT_{50}$)	1:160 in 79% of recipients	no benefit at day 15	very late usage, high rate of seropositives	none	(31)
CTRI/2020/04/024775 (PLACID)	464 (1:1)	BSC	6 (from symptoms)	4-5	200+200	1:40	1:90	no benefit at day 28	moderately late usage; high rate of seropositives; extremely low nAb titre in CCP	none	(10)
NCT04345523 (ConPlas-19)	350 (1:1)	BSC	8 (from symptoms)	3 (25%) 4 (75%)	250-300	1:292	n.a.	no significant differences in primary endpoint (proportion of patients in categories 5, 6 or 7 (death) at 14 days	underpowered for mortality; primary endpoint set at just 15 days	primary endpoint significant at day +28. Trends for reduced overall mortality (p = 0.087) at day +28, expecially in aged > 75 years	(51)
NCT04375098 (Elvira-Balcells)	58 (1:1)	late CCP	6 (from symptoms)	3-4	200+200	≥ 1:160	59% < 1:160 (16% of patients enrolled before day 5 were ≥1:160 vs 60% of	no benefit at day 30 in death, mechanical ventilation or prolonged hospitalization compared to CCP administration only in case of clinical	underpowered, moderately late usage	none	(92)

							those enrolled after day 6	worsening or > 7 days after enrolment			
NCT04383535 (PlasmAr)	333 (2:1)	normal saline	8 (from symptoms)	5	500	1:300 IC_{80}	n.a.	no benefit at day 30 (16.2% vs. 31.2%)	moderately late usage	early arrivals (less than 72 hours) showed superior primary and secondary outcomes in the CCP arm (n= 28) compared to the placebo arm (n=11), but the minimal contribution of this group to the overall cohort (228 CCP and 105 placebo) made the advantage disappear in the final outcomes at day 30 (12).	(12)
NCT04356534 (AlQahtani)	40 (1:1)	BSC	n.a.	4 (95%) 5 (5%)	200+200	n.a.	n.a.	no difference in requirement for ventilation, white blood cell count, LDH, C-reactive protein (CRP), troponin, ferritin, D-dimer, procalcitonin, mortality rate at 28 days	underpowered; the CP group were a higher risk group with higher ferritin levels	primary outcome measure – ventilation – was required in 6 controls and 4 patients on CCP (risk ratio 0.67 95% CI 0.22 – 2.0, p=0.72); mean time on ventilation was 10.5 days in the control against 8.2 days in patients on CCP (p=0.81).	(93)
NCT04346446 (Bajpai)	29 (1:1)	FFP	< 3 (from symptoms)	4-5	250+250	n.a.	n.a.	no significant reduction in mortality or hospitalization	nAb measured with surrogate competitive assay (GenScript); beneficial factors in FFP used in control arm (63)	better median improvement in PaO_2/FiO_2 at 48-hours [42 vs 231] and at day 7	(94)
NCT04381	11558	BSC	9 from	4-7	275±75	n.a.	83%	no significant	late usage	the risk ratio for patients	(30)

936 (RECOVERY)	(1:1)		symptoms; 2 from hospitalization		(81% 2 units from different donors; 12%1 unit)		seronegative	difference in 28-day mortality, progression to invasive mechanical ventilation. Closed for futility		randomized within 7 days of symptom onset was 0.92 in favor of CCP versus 1.06 in patients randomized later. A reanalysis of seronegative patients (having 10% lower mortality) with a vague prior found that the likelihood of any or modest benefit was 90-74% (53).	
NCT04348656 (CONCOR-1)	940 (out of 1200) (2:1)	BSC	8 from symptoms	4-6	1-2 250-ml units	1:250	n.a.	closed for futility (even in the subgroup transfused within 3 days from diagnosis) in intubation or death by day 30	late usage (hypoxemic), sicker CCP arm (more abnormal CXR, more in ICU), varyng standard of care across 72 centres in 3 countries	each standard log increase in neutralization or ADCC independently reduced the potential harmful effect of CCP (OR=0.74), while anti-Spike IgG increased it (OR=1.53)	(81)
NCT02735707 (REMAP-CAP)	1084 (out of 7100?)	n.a.	≤ 3 from ICU hospitalization	5-6	1-2 units	n.a.	n.a.	no significant difference in organ support-free days at day 21 or in-hospital mortality. Closed for futility	very late usage	none	(95, 96)
NCT04355767 (C3PO)	511 (out of 900) with at least 1 risk factor associated with severe COVID-19	BSC	4 from symptoms, presented to the emergency department	2-3	1 250-ml unit	1:641 ID_{50}	n.a.	nonsignificant difference in risk difference (1.9%). Outcomes regarding worst illness severity and hospital-free days were similar in the	'all cause' outcome instead of COVID-19-related outcome; centralized CCP supply to distant sites likely affected by different SARS-CoV-2 variants (35) (since only 4 of the 48 centers were in	9.4% reduction in primary event endpoint in CCP group, which rises to 20% after exclusion on patients admitted on the index visit	(23, 98)

								two groups	Illinois or Colorado, most CCP usage had to be from remote sources); immunosuppressed individuals were nearly twice as common in the treatment group (12.8% vs 6.7%); designed to detect an absolute risk difference of 10% in disease progression (97)		
NCT04359810 (O'Donnell)	223 (2:1)	FFP	9 from symptoms	5-7	1 200-250 ml unit	1:160	n.a.	at 28 days, no significant improvement in clinical status	very late usage; beneficial factors in FFP used in control arm (63)	lower mortality (12.6% vs. 24.6%) compared to nonconvalescent plasma	(11)
NCT04381858 (Gonzalez)	190 (2:1)	IVIg	12 from symptoms	6 7 (85%)	2 200-ml units 24 hours apart	n.a. (29.5% received at least 1 unit of CCP with antibodies)	n.a.	no difference in mortality at day 28	very late usage; beneficial factors of IVIg used in control arm	none	(99)
NCT04344535 (Bennett-Guerrero)	74 (out of 500) (4:1)	FFP	9 from symptoms, 4 from hospitalization	n.a.	2 200-ml units	1:526	n.a.	no difference in ventilator-free days or mortality (27% vs. 33% (at day 28	very late usage; beneficial factors in FFP used in control arm (63)	all-cause mortality through 90 days was numerically lower in the CCP versus standard plasma groups (27% vs 33%; p = 0.63)	(90)
NCT04433910 (CAPSID)	105 (1:1)	BSC	7 from symptoms	4-7	3 units from same donor over 5	1:160 ($PRNT_{50}$)	1:160 ($PRNT_{50}$)	not significant difference in the primary outcome (dichotomous composite outcome	moderately late usage	median time to clinical improvement was 26 days in the CCP group and 66 days in the control group (p=0.27). Median time to	(34)

					days (850 ml)			of survival and no longer fulfilling criteria for severe COVID-19) and secondary outcomes		discharge from hospital was 31 days (IQR 16-n.r.) in the CCP and 51 days (IQR 20-n.r.) in the control group (p=0.24). In the subgroup that received a higher cumulative amount of nAbs the primary outcome occurred in 56.0% (versus 32.1%), with a shorter interval to clinical improvement, shorter time to hospital discharge and better survival compared to the control group	
NCT04547660 (PLACOVID)	160 (1:1)	BSC	10 from symptom	37% 5-6 66% 7	2 300-ml aliquots 2 days apart,	n.a.	>1:80 in 83%	no difference in 28-day mortality, days alive, days free of respiratory support, duration of invasive ventilatory support, inflammatory and other laboratorial markers values on days 3, 7 and 14	very late usage	none	(100)
NCT04429854 (DAWN-plasma)	320 (2:1)	BSC	7 from symptoms	3-5	2 200-250 ml aliquots within 12 hours followe	n.a.	≥1:320	no significant improvement proportion of patients that require mechanical ventilation or have died at day 15 or 30	late usage	none	(101, 102)

					d by 2 units within 36 hours						
NCT04393727 (TSUNAMI)	417 (1:1)	BSC	<10 from onset of symptoms	4-5	2 200-ml aliquots	each unit > 1:160)	n.a.	no statistically significant improvement in progression to ventilatory support or death	late usage	trends favoring CCP in basally seronegatives, P/F > 300 mmHg (p = 0.059),	(103)

* 0: no clinical or virological evidence of infection; 1 : no limitations of activities; 2 : limitations of activities ; 3 : hospitalized, no oxygen therapy; 4 : oxygen by mask or nasal prongs ; 5 : non-invasive ventilation or high-flow oxygen; 6 : intubation and mechanical ventilation ; 7 : ventilation + additional organ support - pressors, RRT, ECMO; 8 : death.

Table 3

Propensity score-matched (PSM) CCP studies reported to date. DPH: days post-hospitalization. None of these studies titered nAbs in either donor or recipient using NT.

time	country	patients+ controls	median days post-hospitalization	baseline recipient WHO score (21)	transfused CCP volume (ml)	statistically significant outcomes	Reason(s) for failure	ref
retrospective	Mount Sinai, NY, USA	39 + 156	4	5 (87%) 6 (10%)	250+250	on day 14 oxygen requirements worsened in 17.9% of plasma recipients versus 28.2% of controls (aOR 0.86). Survival improved in plasma recipients (aHR 0.34)	No failure	(42)
	Providence, RI, USA	64 + 177	> 2 (< 10 from onset of symptoms: median 7)	4 (70%) 5 (30%)	n.a. (2 units)	no significant differences in incidence of in-hospital mortality (12.5% and 15.8%; aHR 0.93) or overall rate of hospital discharge (RR 1.28, although increased among patients > 65-years)	Late usage	(45)
	Montefiore Medical Center, NY, USA	90 + 258	< 3 (3-7 days from onset of symptoms)	5-6 (< 24 hrs mechanical ventilation)	200	anti-S IgG titer ≥1:2,430 (median 1:47,385) recipients <65 years had 4-fold lower mortality and 4-fold lower deterioration in oxygenation or mortality at day 28	No failure	(41)
	Washington, USA	263+263	< 14	n.a.	245 (median)	reduced 7-day (9.1 vs. 19.8%) and 14-day mortality (14.8 vs. 23.6%), but not 28-day mortality (P = 0.06), and longer hospital stay	Late usage; control cohort was treated, on average, 29 days prior to the CCP cohort	(47)
	USA (176 HCA Healthcare-affiliated community hospitals)	3774 + 10687	< 3 vs. 4-7	n.a.	n.a.	lower mortality (aHR = 0.71) and faster recovery. CCP within 3 days after admission, but not 4-7 days, was associated with a significant reduction in mortality risk (aHR = 0.53). CCP serology level was inversely associated with mortality when controlling for interaction with days to transfusion (HR = 0.998) but was not significant in a univariable analysis	No failure	(48)
	China	163 + 163	23	n.a.	300	hospital stay in CCP group was significantly longer than matched control group ($P < 0.0001$).	Very late usage; more advanced disease in the CCP group (23 days vs.	(104)

							15 since hospital admission	
	Greece	59 + 59	7	≥ 4	200-233 ml (days 1, 3, and 5)	significantly reduced risk of death [HR: 0.04, 3.4% vs. 13.6%], significantly better overall survival by Kaplan-Meir analysis, and increased probability of extubation [OR: 30.3]. Higher levels of antibodies (as measured with Euroimmun or pseudoVNT) in CCP were independently associated with significantly reduced risk of death.	No failure	(105)
	New Haven, USA	132 + 2551	< 6 vs > 6 days	moderate to severe		early CCP recipients, of whom 31 (40%) were on mechanical ventilation, had lower 14-day (15% vs 23%) and 30-day (38% vs 49%) mortality compared to a matched unexposed cohort, with nearly 50% lower likelihood of in-hospital mortality (HR 0.52). Early plasma recipients had more days alive and ventilator-free at 30 days (+3.3 days) and improved WHO scores at 7 days (-0.8) and hospital discharge (-0.9) compared to the matched unexposed cohort	No failure	(46)
	USA	143+823 (hematogical cancer)	n.a.	n.a.	n.a.	improved 30-day mortality (HR, 0.52; 95% CI, 0.29-0.92). Among the 338 patients admitted to the ICU, mortality was significantly lower in CCP recipients compared with nonrecipients (HR 0.40). Among the 227 patients who required mechanical ventilatory support, mortality was significantly lower in CCP recipients compared with nonrecipients (HR 0.32).	No failure	(76)
prospective	Houston, USA	136 + 251	n.a.	3 (9%) 4 (63%) 5 (18%) 6 (10%) 7 (1%)	300 (1-2 units)	reduction in mortality within 28 days, specifically in patients transfused < 72 hours of admission with CCP with an anti-RBD titer ≥1:1350 (i.e., ~80% probability of a live virus *in vitro* neutralization titer of ≥1:160 (106))	No failure	(43)
		341 + 594	n.a.		300 (1-2 units)	reduced 28-day (aHR=2.09 for controls) and 60-day (5.7% vs. 10.7%; aHR=1.82 for controls) mortality in those transfused with anti-RBD ≥1:1350 within 72 hours	No failure	(44)

						post-hospitalization. Optimal window of 44 hours to maximize benefit in 60 days mortality (4% vs 12.3%). 91% received CCP with an anti-RBD titer ≥1:1350. median S/CO ratio =24 using Ortho Vitros.		
	Poland	102 + 102	n.a.	n.a.	n.a.	lower mortality rate (13.7% vs. 34.3%; OR=0.25) related to time of first administration (12.2% at day 5, 21.5% at day 10), no significant differences in ICU stay, ventilator time, and hospitalization time. Earlier administration resulted in a ventilator being needed for a shorter length of time (r = 0.41)	No falure	(107)
	Colorado (16 hospitals)	188 + 188	n.a.	n.a.	1 unit if < 90 kg; 2 units if > 90kg	increased length of hospital stay in CCP-treated patients and no change in inpatient mortality compared to controls. In subgroup analysis of CCP-treated patients within 3 or 7 days of admission, there was no difference in length of hospitalization and inpatient mortality.	Covariate matching not achieved for subgroup receiving CCP < 3 days	(108)

Table 4

Summary of completed but not yet reported or ongoing RCTs of CCP, as registered on ClinicalTrials.gov as of August 26, 2021. BSC: best supportive care; FFP: fresh frozen plasma. Several studies were withdrawn (NCT04377568).

Status	NCT number	Patient subtype	Control arm	Study design	Number planned to enrol	Study start	Locations
Completed	NCT04332835	severe (SOFA <6)	BSC	single masking (outcomes assessor)	92	August 8, 2020	Colombia
	NCT04349410	any	10 different arms	single masking (investigator)	1800	April 11, 2020	USA
	NCT04397757	ordinal scale 5 to 7	BSC	open label	80	May 30, 2020	USA
	NCT04421404	within 3 days from hospitalization or 14 from symptoms	placebo	triple masking (participant, care provider, investigator)	34		USA
	NCT04374526	pneumonia, age > 65 and PaO2/FiO2 ≥300 mmHg and comorbidities	BSC	open label	29	May 27, 2020	Italy
	NCT04358783	hospitalized requiring supplemental oxygen	BSC	quadruple masking (participant, care provider, investigator, outcomes assessor)	30	April 27, 2020	Mexico
	NCT04405310	moderate to severe requiring supplemental oxygen	albumin	double (participant, care provider)	80	May 20, 2020	Mexico
	NCT04425915	on ventilator within 3 days from onset of symptoms	BSC	open label	400	June 14, 2020	India
Active, not recruiting	NCT04539275	ventilated and within 3 days from hospitalization	masked saline placebo	triple masking (participant, care provider, investigator)	702	November 16, 2020	USA
	NCT04374487	hospitalized and severe	BSC	open label	100	May 9, 2020	India
	NCT04323800	exposed within 96 h	FFP	triple masking (participant, care provider, investigator)	500	June 10, 2020	USA

		of enrollment and 120 h of receipt of CCP					
	NCT04364737 (CONTAIN)	hospitalized and within 7 days from symptoms	placebo	double masking (participant, investigator)	300	April 17, 2020	USA
	NCT04425837	high-risk	BSC	single masking (outcomes assessor)	236	July 2020	Colombia
	NCT04395170	hospitalized	2 arms (BSC; anti-COVID-19 IVIG)	open label	75	September 2020	Colombia
	NCT04391101	severe	BSC	open label	231	June 2020	Colombia
Recruiting	NCT04516811	moderate to severe	placebo	triple masking (participant, care provider, investigator)	600	September 21, 2020	South Africa
	NCT04388410	hospitalized, severe disease or risk for severe diseases	BSC	quadruple masking (participant, care provider, investigator, outcomes assessor)	410	August 25, 2020	Mexico
	NCT04385043	severe Infection	BSC	open label	400	May 1, 2020	Italy
	NCT04380935	acute respiratory distress syndrome	BSC	open label	60	May 18, 2020	Indonesia
	NCT04362176 (PassItOn)	hospitalized adults	placebo	triple masking (participant, care provider, outcomes assessor)	1000	April 24, 2020	USA
	NCT04390503	exposed within 7 days or mild symptoms within 5 days	albumin	double masking (participant, outcome assessor)	150	March 12, 2021	USA
	NCT04376034	severe or life-threatening	BSC	open label	240	March 30, 2021	USA
	NCT04373460	outpatients within 8 days from symptoms	FFP	triple masking (participant, care provider, outcomes assessor)	1344	June 3, 2020	USA
	NCT04366245	hospitalized ventilated	BSC	open label	72	April 23, 2020	Spain
	NCT04333251	hospitalized within 7 days from symptoms	BSC	open label	115	April 1, 2020	USA
	NCT04345991	mild and within 8	BSC	open label	120	April 15, 2020	France

		days from symptoms					
	NCT04372979	hospitalized within 10 days from symptoms	FFP	triple masking (participant, care provider, outcomes assessor)	80	September 14, 2020	France
	NCT04345289	adults with pneumonia	placebo	quadruple masking (participant, care provider, investigator, outcomes assessor)	1100	May 1, 2020	Denmark

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