Efficacy of Convalescent Plasma (CP) and COVID-19

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Background: The first passive immunity strategy used to treat patients with active COVID-19 infections was convalescent plasma, initiated in February 2020 when no other treatment was available. By the summer of 2020, CP was being deployed at scale in the United States, with at least one half million patients treated. As the pandemic progressed in 2020, consistent with the well-established principles of antibody therapy, clinicians at the bedside used high titer CP early in the course of disease. An epidemiologic analysis correlating CP use and mortality suggests that CP saved as many as 100,000 lives in the USA.

As the pandemic continued, information from an impressive array of randomized controlled trials, retrospective studies, case series, and case reports defined the parameters associated with effective use of CP. *A holistic view of the entirety of the data indicates that if sufficient antibodies are administered early in the course of disease, disease progression can be limited, and a mortality benefit may be seen. The loss of efficacy of monoclonal antibodies against newer COVID variants also means that very high titer CP harvested from donors who are both recently infected and vaccinated is the only antibody therapy available that can evolve in real time with the virus.*

Outpatient Trials: Four major outpatient trials all show signals of efficacy for CP. The Libster Trial in the NEJM and the Hopkins Trial posted as a preprint both administered high titer plasma to patients very early after symptom onset and diagnosis and reduced hospital admissions and/or clinical progression by ~50%. The C3PO study was reported as negative but an inordinately large number of patients in the plasma treatment arm were admitted to hospital (a key outcome measure) on the same day they received plasma. When those patients are excluded, CP administration reduced admissions by ~35%. A report from Europe that combined two similar trials that were terminated early due to slowing enrollment as the first wave of the pandemic waned reported evidence that CP administered within five days of symptom onset reduced hospital admissions and death, even though that trial used plasma whose efficacy might have been impaired by procedures to sterilize the product.

Summary of Outpatient Trials: *Two of four outpatient trials of CP clearly demonstrate efficacy. When design and analysis issues are considered, all four trials demonstrate some degree of efficacy. These data should also be viewed in the context of 1) the loss of efficacy of some monoclonal antibodies, and 2) observations indicating that plasma from individuals who have been infected and vaccinated or experienced breakthrough infections is likely effective against a wide array of variants.* The Infectious Disease Society of America guidelines have recently been updated to support the outpatient use of CP in some circumstances.

Inpatient Trials: Five major inpatient trials were reported relatively early in the course of the pandemic. While categorized as having overall "negative" findings, all five trials violated the principles of antibody therapy by either focusing on later use and/or in some cases, using CP deficient in antibodies. In essence these trials tested CP in patients where it was unlikely to work and then concluded that it was ineffective, creating a cycle that inappropriately reinforced futility. But signs that CP works when used appropriately were found in all.

The large RECOVERY trial demonstrated signals of efficacy in patients requiring minimal supplemental oxygen, not on steroids and/or treated within seven days of diagnosis. Both the Simonovich and Agarwal trials demonstrated symptomatic improvement with CP treatment. CONCOR-1 showed a clear dose response curve with improved outcomes with the highest quality plasma. REMAPCAP showed evidence of benefit with early treatment and in immunosuppressed patients.

More recently trials continue the pattern. TSUNAMI reported no overall benefit, but clear evidence of efficacy in less severely ill patients treated early. CONTAIN shows evidence of efficacy – especially early in the pandemic – in patients with less severe disease. Detailed commentaries and critiques of these and other trials are available at https://ccpp19.org/news/index.html. Examples of RCT's that clearly show benefit when high titer plasma is given early include the trials first-authored by O'Donnell, Bar, and Körper.

Summary of Inpatient Trials: *All major negative RCTs show signals of efficacy especially in subgroups whose treatment was aligned with the principles of antibody therapy. RCTs that tested the earlier use case and/or higher doses of plasma have been more uniformly positive.* A validated Treatment Benefit Index calculator has been developed (and can be found on the CCPP19 website). It used a patient level meta-analysis to identify inpatients most likely to benefit from CP.

Tables 1 & 2 are Chalmers style analyses of the papers just reviewed and data from additional trials categorized by optimal and suboptimal use of CP.

Retrospective Matched Control Trials: A number of retrospective matched control studies have been performed. These have been graphically summarized and in general demonstrate a relative mortality benefit of 25-50% when – consistent with the principles of antibody therapy - high titer plasma is administered early in the course of hospitalization. Two of the most sophisticated analyses include a large nationwide real world data set from the Hospital Corporation of America and also data from Houston Methodist Hospital. The high-titer early-use case is also supported by data from the US EAP. Two additional large EAP-like studies from Argentina and Italy yielded similar observations that early use of CP in hospitalized patients was associated with reduced mortality.

Immunosuppressed Patients: There are numerous case series and case reports showing that CP can have dramatic effects when administered as *replacement therapy* to patients who are unable to generate endogenous antibodies. These have been summarized as of the middle of 2021 with an update in the progress. Importantly, two matched control trials (one from the US and one from France) focused primarily on B-Cell depleted COVID-19 patients with heme-malignancies demonstrate a marked mortality benefit when patients are treated with CP.

Additional Considerations: Plasma obtained in close proximity to where it is to be used has increased efficacy. Numerous sources suggest that CP obtained from individuals who have recovered from infection and been vaccinated or experienced breakthrough infections is extremely high titer and covers a wide array of variants. This "hybrid" or "Vax" plasma appears to be widely available in the standard blood donor pool and the number of potential donors is almost certainly increasing dramatically.

Overall Summary: Convalescent Plasma when used in a manner consistent with the principles of antibody therapy is effective in reducing disease progression and mortality in patients with COVD-19. As the pandemic continues, very high titer and "broad spectrum" plasma will become increasingly available from the many donors who have both recovered from disease and been vaccinated or from vaccinated donors who have experienced breakthrough infections.

It is critically important to note that in contrast to monoclonal antibodies, recently obtained CP is likely to be effective with novel variants. The use case for CP as replacement therapy for patients unable to generate endogenous antibodies is especially strong. CP is also potentially available worldwide. Two years into the COVID-19 pandemic, the knowledge base, experience, and potential supply of CP means that it can be used optimally during the next phases of the pandemic and when COVID-19 becomes endemic. Many lessons have been learned that can be applied in preparation for future outbreaks of novel infectious diseases.

Table 1.*

Mortality rates among randomized clinical trials of optimal use convalescent plasma therapy for COVID-19

	Convalescent Plasma			Control					
Study	**Survivor**	**Non-Survivor**	**Mortality**	**Survivor**	**Non-Survivor**	**Mortality**	**Mechanical ventilation (%)**	**Titer**	**Time to transfusion (days)**
Avendaño-Solà et al.	172	7	4%	157	14	8%	0%	High titer	1 (admission)
Bar et al.	38	2	5%	29	10	26%	0%	High titer	1 (admission)
Bennett-Guerrero et al.	43	16	27%	10	5	33%	19%	High titer	4 (admission)
Devos et al.	310	10	3%	155	8	5%	0%	High titer	7 (symptoms)
Gharbharan et al.	37	6	14%	32	11	26%	12%	High titer	2 (admission)
Korper et al.	42	11	21%	35	17	33%	30%	High titer	2 (admission)
Libster et al.	78	2	3%	76	4	5%	0%	High titer	3 (symptoms)
Menichetti F et al.	217	14	6%	221	19	8%	0%	High titer	7 (symptoms)
O'Donnell et al.	131	19	13%	55	18	25%	11%	High titer	9 (symptoms)
Ortigoza et al. (No corticosteroids subgroup)	85	9	10%	69	18	21%	0%	High titer	1 (admission)
Simonovich et al.	197	25	11%	93	12	11%	0%	High titer	8 (symptoms)
Sullivan et al.	592	0	0%	289	3	1%	0%	High titer	6 (symptoms)
The CONCOR-1 Study Group (high titer subgroup)	268	75	22%	133	40	23%	0%	High titer	5 (diagnosis)
The RECOVERY Collaborative Group (No corticosteroids subgroup)	317	74	19%	313	100	24%	5%	High Titer	2 (admission)
The REMAP-CAP Investigators (Moderate state subgroup)	54	8	13%	17	7	29%	0%	High titer	2 (admission)
The SIREN-C3PO Investigators	256	5	2%	253	1	0%	0%	High titer	4 (symptoms)
Overall	**2837**	**283**	**9.1%**	**1937**	**287**	**12.9%**			

$\chi^2 = 20.13$, $P < 0.001$; 41.7% relative mortality reduction associated with convalescent plasma therapy

Table 2.

Mortality rates among randomized clinical trials of non-optimal use convalescent plasma therapy for COVID-19

	Convalescent Plasma			Control					
Study	**Survivor**	**Non-Survivor**	**Mortality**	**Survivor**	**Non-Survivor**	**Mortality**	**Mechanical ventilation (%)**	**Titer**	**Time to transfusion (days)**
Agarwal et al.	201	34	14%	198	31	14%	8%	Not high titer	4 (admission)
Ali Shaukat et al.	30	10	25%	4	6	60%	3%	Not high titer	8 (symptoms)
AlQahtani et al.	19	1	5%	18	2	10%	0%	-	-
Bajpai et al.	11	3	21%	14	1	7%	0%	Not high titer	3 (symptoms)
Bandopadhyay et al.	30	10	25%	26	14	35%	-	Not high titer	-
Gonzalez et al.	60	70	54%	28	32	53%	85%	-	-
Kirenga B et al.	59	10	14%	59	8	12%	0%	-	7 (symptoms)
Li et al.	43	8	16%	38	12	24%	30%	Not high titer	33 (symptoms)
Ortigoza et al. (Corticosteroids subgroup)	334	17	5%	333	24	7%	0%	High titer	1 (admission)
Pouladzadeh et al.	27	3	10%	25	5	17%	10%	Not high titer	0 (admission)
Rasheed et al.	20	1	5%	20	8	29%	81%	Not high titer	4+ (admission)
The CONCOR-1 Study Group (not high titer subgroup)	205	66	24%	101	23	19%	0%	Not high titer	5 (diagnosis)
The RECOVERY Collaborative Group (Corticosteroids subgroup)	4056	1314	24%	4012	1299	24%	5%	High titer	2 (admission)
The REMAP-CAP Investigators (Severe state subgroup)	679	407	37%	557	347	38%	0%	High titer	2 (admission)
Sekine et al.	62	18	23%	67	13	16%	30%	Not high titer	10 (symptoms)
Overall	**5836**	**1972**	**25.3%**	**5500**	**1825**	**24.9%**			

$\chi^2 = 0.23$, $P = 0.63$; - indicates data not available

**Analysis performed by S. Klassen, PHD and J. Senefeld, PHD*