Should convalescent plasma be used in the treatment of COVID-19 in pediatric patients?

Authors: Ralph Geoffrey Manzon MD, Sittie Janessa D. Dalidig MD, Anna Lisa Ong-Lim MD, Leonila F. Dans MD
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KEY FINDINGS

- There are no studies yet as to the effectiveness of convalescent plasma therapy in the treatment of COVID-19 in pediatric patients; however, indirect evidence from adult studies present evidence of significant antiviral activity against COVID-19.

- There are no existing reports yet on the effectiveness of convalescent plasma for COVID-19 patients in the pediatric population.
- There were 18 published studies among the adult population that utilized plasma therapy for patients with COVID-19. Two randomized controlled trials were judged to be of moderate risk of bias due to indirect provision of evidence for the pediatric population. The other observational studies, however, are at serious to critical risk for bias through the lack of control groups, small sample sizes, and selection criteria for treated patients.
- There were a total of 282 patients in these 18 studies; among these studies, the majority (251/282, 89.0%) had improved conditions post-transfusion.
- Multiple adverse events, mostly due to transfusion-related allergic reactions, have been recorded, but most of them are transient and promptly resolved with appropriate supportive management.
- Overall, it can be indirectly concluded that convalescent plasma may offer antiviral activity through host-mediated increase in antiviral antibodies as well as passive immunization from the donor plasma.
- There are currently seven studies ongoing for the use of convalescent plasma in pediatric COVID-19 patients, and the results are yet to be published.
- In PGH, guidelines for compassionate use of convalescent plasma in COVID-19 patients are already available, with pediatric populations included as recipients whenever deemed necessary by the attending physician.

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RESULTS

As of 15 July, 2020, there is no existing report yet on the effectiveness of convalescent plasma for COVID-19 patients in the pediatric population.

Evidence was thus indirectly obtained from 18 published studies among the adult population that utilized plasma therapy for patients with COVID-19. (Jin et al., 2020) (Duan et al., 2020) (Pei et al., 2020) (Shen et al., 2020) (Tan et al., 2020) (Xu et al., 2020) (Ye et al., 2020) (Zhang et al., 2020) (Zhang et al., 2020) (Anh et al., 2020) (Im et al., 2020) (Anderson et al., 2020) (Salazar et al., 2020) (Liu et al., 2020) (Rasheed et al., 2020) (Madriaga et al., 2020) (Gbarbharan et al., 2020) (Li et al., 2020). Two randomized controlled trials were judged to be of moderate risk of bias due to indirect provision of evidence for the pediatric population. The other observational studies, however, are at serious to critical risk for bias through the lack of control groups, small sample sizes, and selection criteria for treated patients.

There were a total of 282 patients in these 18 studies; among the observational studies, the majority (173/177, 97.7%) had improved conditions post-transfusion ranging from discontinuation of invasive mechanical ventilation, resolution of radiographic lesions, decreases in inflammatory markers, generation and marked increase in neutralizing antibodies, and negative turnout in cycle threshold levels on PCR; these patients were eventually discharged or transferred to non-critical wards. For the non-observational studies, majority of the patients (78/105, 78.1%) similarly improved. Mortalities recorded were related to thromboembolic events consistent with COVID-19 symptoms (Salazar et al., 2020), as well as cases who eventually succumbed to end stages of the COVID disease (Gharbharan et al., 2020) (Li et al., 2020) (Liu et al., 2020) (Madriaga et al., 2020) (Rasheed et al., 2020).

Multiple adverse events have been noted in these studies. In the RCT study, two patients developed transfusion-related allergic reactions (chills and rashes, and dyspnea), but were promptly resolved through dexamethasone, promethazine, aminophylline, and other supportive care measures (Li et al., 2020). One study detailed the development of an evanescent facial erythema in one out of 10 treated patients, which subsequently resolved without needing any other intervention. (Duan et al., 2020) Anaphylactic shock was reported in the 51-year old female about 30 mL into transfusion; whether the patient was dead or alive was not reported. (Pei et al., 2020) In the cohort of 25 patients, there were incidents of morbilliform rash, deep vein thrombosis, and deep vein thrombosis with pulmonary embolism. (Salazar et al., 2020) However, the thrombotic complications were attributed to the disease entity itself, as reported in the literature. (Klok et al., 2020)

Seven clinical trials are currently registered, with two of these solely focused on hospitalized children. Outcomes are yet to be determined and published. Appendix 2 summarizes the ongoing pediatric clinical trials.

CONCLUSION

No studies have been found that targeted the pediatric population for convalescent plasma therapy for COVID-19. However, indirect evidence from a few cited studies on adult COVID-19 patients have shown that convalescent plasma offers significant antiviral activity against the viral infection through host-mediated increase in antiviral antibodies as well as passive immunization from the donor plasma. Duration of clinical, laboratory, and radiological improvements vary among patient to patient, and can be influenced by concurrent therapies, donor selection, timing of intervention, and the natural immunity of the patient.

Further studies are necessary to establish the effective and safe use of convalescent plasma. There are ongoing pediatric clinical trials exploring this intervention. Indirect evidence from the adult population may be boosted through larger-scale trials, but such studies remain to be published. Nonetheless, reviewing the data from studies where convalescent plasma was used for treatment among adult patients, compassionate use of this intervention can be considered as an experimental option in severe to critical pediatric COVID-19 cases. As this is an experimental therapy, supportive measures must have been exhausted beforehand.

Declaration of Conflict of Interest

No conflict of interest

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Table 1. Characteristics of included studies

Authors, Month and year of publication	Title of the study	Participant characteristics	Comorbidities	Dose of convalescent plasma	Outcomes (*days post-transfusion)*	Imaging *(days post-transfusion)*	Adverse events
Anderson et al., May 2020	The use of convalescent plasma therapy and remdesivir in the successful management of a critically ill obstetric patient with novel coronavirus 2019 infection: A case report	Age 35 One female	22 weeks, 2 days age of gestation	Not specified	No significant effects noted; after initiation of remdesivir, however, noted relief from ventilatory support (5 days after)	None reported	None reported
Anh et al., Apr 2020	Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea	Median age 69 One male, one female	Hypertension (1)	250 mL q12 for two doses	-Decrease in fever and oxygen demand -Decreased CRP, IL-6 to normal (earliest after 1 day) --Marked increase in lymphocytes, decrease in leukocytes -Relief from ventilator support (earliest after 9 days) -Negative for COVID-19 (earliest after 9 days)	Marked decrease bilateral lung infiltrates (earliest after 4 days)	None reported
Jin et al., June 2020	Treatment of Six COVID-19 Patients with Convalescent Plasma	Median age 60 Four males, two females	Diabetes mellitus (2), hypertension (2), coronary heart disease (2), cerebrovascular disease (2), renal artery stenosis (1)	200 mL	-Negative for COVID-19 (earliest after 2 days) - Decrease in CRP, IL-6, and procalcitonin -Increase in lymphocytes and monocytes - Increase in PaO_2/FiO_2 1 still hospitalized	Variable absorption of lung lesions (earliest after 2 days)	None reported

					1 remains COVID-19 positive		
Duan et al., April 2020	Effectiveness of convalescent plasma therapy in severe COVID-19 patients	Median age 52.5 Six males, four females	Hypertension (4), cerebrovascular disease (1), cardiovascular disease (1)	200 mL for single dose	-Marked improvement/lysis of fever, difficulty in breathing (earliest after91 day) -Relief from oxygenation support -Increase in lymphocytes, decrease in CRP, improvement in SaO2 -Increase in neutralizing antibodies -Negative for COVID-19 (earliest after 1 day)	-Varying degrees of ground glass opacities (earliest after 3 days)	-One patient had evanescent facial erythema, spontaneously resolving
Gharbharan et al., July 2020	Convalescent Plasma for COVID-19. A randomized clinical trial	Median age 61 29 males, 14 females	Diabetes mellitus (13), hypertension (11), cardiac (9), pulmonary (12), cancer (5), immunodeficiency (5), CKD (1), cirrhosis (1)	300 mL for single dose	No difference in mortality (p=0.95) hospital stay (p=0.68) or day-15 disease severity (p=0.58) 5 patients died	None reported	None reported
Im et al., July 2020	Convalescent Plasma Therapy in Coronavirus Disease 2019: a Case Report and Suggestions to Overcome Obstacles	Age 68 One male	Not reported	250 mL for two doses	- Decrease in fever and respiratory distress (3 days after) - Improvement in PaO_2/FiO_2	- Improvement of pneumonia (3 days after)	None reported
Li et al., June 2020	Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A	Median age 70 60 males, 43 females	Hypertension (56), cardiovascular disease (26), cerebrovascular disease (18), diabetes (21), liver disease (10), cancer (3), kidney disease (6)	200-300 mL for single dose	- no significant difference in the primary outcome of time to clinical improvement within 28 days: 51.9% (27/52) in the convalescent plasma group vs 43.1%	- none reported	- Two patients had transfusion related allergic reactions improving with supportive care

	Randomized Clinical Trial				(22/51) in the control group - no significant difference in the secondary outcome of 28-day mortality (15.7% in the convalescent plasma group vs 24.0%in the control group; OR, 0.65 [95%CI, 0.29-1.46]; P = .30) - no significant difference in the secondary outcome of time from randomization to discharge (51.0% in the convalescent plasma group vs 36.0% in the control group were discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93];P = .12) - rates of negative SARS-CoV-2 viral PCR in the convalescent plasma group were all significantly higher than that of the control group (44.7%vs 15.0%, P = .003 at 24 hours; 68.1% vs 32.5%, P = .001 at 48 hours; 87.2%vs 37.5%, P < .001 at 72 hours) 8 patients died		
Liu et al., May 2020	Convalescent plasma treatment of severe COVID-19: A matched control study	Mean age: 55 25 males, 14 females	Asthma (3), cancer (2), chronic kidney disease (1), chronic obstructive pulmonary disease (1), diabetes mellitus (8), obesity (21),	250 mL for two doses	- more likely to remain or have improvements in their supplemental oxygen requirements by post-transfusion day 14, [OR 0.86 (95% CI: 0.75~0.98; p=0.028)]	- Not further discussed	None reported

			obstructive sleep apnea (2)		- improved survival, compared to control patients (log-rank test: p=0.039) - improved survival for non-intubated patients (hazard ratio 0.19 (95% CI: 0.05 ~0.72); p=0.015), but not for intubated patients (1.24 (0.33~4.67); p=0.752). 8 patients died		
Madariaga et al., June 2020	Clinical predictors of donor antibody titer and correlation with recipient antibody response in a COVID-19 convalescent plasma clinical trial	Mean age 61.9 Six males, four females	Not reported	300 mL for single dose	-Relief from oxygenation support - Improvement of SOFA scores - Wean off from vasopressor support (earliest 7 days) -recipient anti-RBD antibody titer increased on average by 31% per day (p=0.01) and recipient anti-spike antibody titer increased on average by 40.3% per day (p=0.01) - duration of illness was lower than in control group, (19.3±6.9 vs 23.42±6.4 days (P<0.05) 1 patient remained hospitalized 1 patient died after transfer to comfort care facility	- None reported	None reported
Rasheed et al., June 2020	The therapeutic effectiveness of Convalescent plasma therapy on treating	Mean age: 55 12 males, 9 females (therapy	Not reported	Not indicated	- recovery time from critical illness in CP group was lower than that in control group	None reported	- Mild skin redness and itching lasting for 1 hr

	COVID-19 patients residing in respiratory care units in Baghdad, Iraq	group) 28 matched controls			(4.52±2.3 vs 8.45±1.8 days (P<0.01) - no significant difference in the percentage of patients on ventilators in CP versus in control groups (81% vs 57% (P>0.05) - IgM and IgG positivity at D3 was higher in CP group vs control group (P<0.05) lower rate of mortality 1/21 (4.8%) patient in CP group died versus 8/28 (28.5%) in control group (P<0.05)		
Pei et al., April 2020	Convalescent Plasma to Treat COVID-19: Chinese Strategy and Experiences	Median age: none reported; one patient 51 year-old Sexes: cannot be determined, one patient female Three patients overall	None reported	200-500 mL for six-eight doses	- Improvement of clinical symptoms (days post-transfusion not reported) - Negative for COVID-19 (earliest after four days)	- Not reported	- Anaphylactic shock after 30 mL convalescent plasma transfusion
Salazar et al., May 2020	Treatment of COVID-19 Patients with Convalescent Plasma in Houston, Texas	Median age 51 11 males, 14 females	Obesity (17), diabetes (10), Hypertension (9), Hyperlipidemia (5), Gastrointestinal reflux disease (4), Atrial fibrillation (1), Chronic kidney disease (1), Postpartum hypothyroidism (1),	300 mL for single dose, except for one patient given additional dose six days post-transfusion	- Improvement from baseline condition, measured as discharge or 1-point improvement on a modified clinical scale from day 0 to day 14 - 36% (9/25) of patients had improved (day 7 post-transfusion) - 76% (19/25) of patients had improved (day 14 post-transfusion)	- None reported	- Morbilliform rash (1) - Deep vein thrombosis (2) - Deep vein thrombosis and pulmonary embolism (1)

					- average overall length of hospital stay 14.3 days (2-25 days) - average post-transfusion length of hospital stay 11 days (1 -21 days) - median decrease in C-reactive protein -14.21 mg/dL (day 14 post-transfusion) - median decrease in ferritin -160 ng/mL (day 14 post-transfusion) - median decrease in LDH -75 U/L (day 14 post-transfusion) Mortality: 1 patient (conditions not disclosed in the paper)		
Shen et al., March 2020	Treatment of 5 critically ill patients with COVID-19 with convalescent plasma	Median age 60 Three males, two females	Hypertension and mitral insufficiency (1)	200-250 mL for two doses	-Improvement of fever (1-12 days) -Decrease in CRP (7-12 days), decrease in procalcitonin (12 days), decrease in IL-6 (12 days) -Pao2/Fio2 improved (1-7 days) -Steady increase in IgG, IgM, and neutralizing antibodies as early as 1 day -Relief from oxygen support (2-9 days), but two patients remain on mechanical ventilator support -Negative for COVID-19 (1-12 days), but two patients remain hospitalized	-Improvement of radiologic lesions (within 3 days)	None reported

Tan et al., March 2020	A special case of COVID-19 with long duration of viral shedding for 49 days	Age 40-50 years old One male	None reported	400 mL for single dose	- Negative for COVID-19 (two days after)	None reported	- Fever, resolving after one day
Xu et al., June 2020	Non-optimal effectiveness of convalescent plasma transfusion and hydroxychloroquine in treating COVID-19: a case report	Age 65 One male	None reported	Not specified	- Disappearance of viremia (seven days after) - Relief from oxygenation support (11 days after)	Resolution of lesions (after 32 days)	None reported
Ye et al., April 2020	Treatment with convalescent plasma for COVID-19 patients in Wuhan, China	Median age 60 Three males, three females	Sjogren's syndrome (1)	200 mL for 1-3 doses	-Relief of symptoms (1 day) -Increase in IgG and IgM (1-3 days) -Negative for COVID-19 (1-13 days)	-Improvement of radiologic lesions (3-13 days)	None reported
Zhang et al., April 2020	Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection	Median age 62 Two males, two females	Hypertension (1), renal failure (1), pregnancy (1)	200 mL - 400 mL for 1-8 doses	-Relief from oxygen support (1-15 days) -Decrease in viral load (10-11 days) -Development of IgG antibodies (~14 days) -Relief from oxygen support (20 days) -Negative for COVID-19 (3-22 days), but one patient remain hospitalized	-Improvement of radiologic lesions (1-10 days)	None reported
Zhang et al., April 2020	Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19	Age 64 One female	Hypertension, diabetes	200 mL for single dose	- Relief from mechanical ventilation (11 days)	None reported	None reported

Table 2. Characteristics of clinical trials

Title of clinical trial	Sponsor	Intervention model	Study phase	Primary Outcomes	Secondary Outcomes	Study arms	Estimated start date/end date	Title of clinical trial	Sponsor
Efficacy of Human Coronavirus-immune Convalescent Plasma for the Treatment of COVID-19 Disease in Hospitalized Children (CONCOR-KIDS)	The Hospital for Sick Children	Randomized control trial	Phase 2	Clinical recovery	-Combined mortality/intubation Respiratory status (intubation proprtion, time to intubation, mean number of ventilator-free days, mean number of ventilator days, oxygen free days, ECMO proportion) -Mortality (time to in-hospital death, proportion of patients with survival status) -Care and critical care (length of hospitalization, length of ICU stay) -Morbidities (need for renal replacement therapy, myocarditis, transfusion associated adverse events, cumulative incidence of adverse events)	-Convalescent plasma + standard of care -Standard of care	May 1, 2020/December 1, 2021	Efficacy of Human Coronavirus-immune Convalescent Plasma for the Treatment of COVID-19 Disease in Hospitalized Children (CONCOR-KIDS)	The Hospital for Sick Children

Human Convalescent Plasma for High Risk Children Exposed or Infected With SARS-CoV-2 (COVID-19)	Johns Hopkins Hospital	Single group	Phase 1	Safety of treatment with high-titer anti-SARS-CoV-2 plasma as assessed by adverse events	-Proportion of subjects with disease worsening event -Anti-SARS-CoV-2 antibody titer changes -Proportion of subjects with a natural antibody response to SARS-CoV-2 infection	Anti- SARS-CoV-2 Plasma	May 18, 2020/May 21, 2021	Human Convalescent Plasma for High Risk Children Exposed or Infected With SARS-CoV-2 (COVID-19)	Johns Hopkins Hospital
Convalescent plasma for ill patients by COVID-19 (COPLASCOV 19)	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado	Single group	Phase 1 Phase 2	-Clinical improvement -improvement in tomographic image -test positivity for COVID-19 -early and late complications associated to convalescent plasma	-Length of ICU stay	-one severely ill (not intubated) and one very severely ill (intubated)	May 2020/November 2020	Convalescent plasma for ill patients by COVID-19 (COPLASCOV 19)	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado
SARSCoV2 (COVID-19) Convalescent Plasma (CP) Expanded Access Protocol (EAP)	AdventHealth	Expanded access	Expanded access	N/A	N/A	N/A	First posted May 1, 2020	SARSCoV2 (COVID-19) Convalescent Plasma (CP) Expanded Access Protocol (EAP)	AdventHealth
Treatment Of CORONAVIRUS DISEASE 2019 (COVID-19) With Anti-Sars-CoV-2 Convalescent	U.S. Army Medical Research and Development Command	Expanded access	Expanded access	N/A	N/A	N/A	First posted April 24, 2020	Treatment Of CORONAVIRUS DISEASE 2019 (COVID-19) With Anti-Sars-CoV-2 Convalescent	U.S. Army Medical Research and Development Command

Plasma (ASCoV2CP)								Plasma (ASCoV2CP)	
Evaluation of SARS-CoV-2 (COVID-19) Antibody-containing Plasma thErapy ((ESCAPE))	Brigham and Women's Hospital	Randomized control trial	N/A	Modified WHO Ordinal Scale (MOS) score	N/A	-Arm A: High-Titer COVID-19 Convalescent Plasma (HT-CCP) -Arm B: Standard Plasma (FFP)	April 2020/December 2021	Evaluation of SARS-CoV-2 (COVID-19) Antibody-containing Plasma thErapy ((ESCAPE))	Brigham and Women's Hospital
Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19	Shanghai Public Health Clinical Center	Observational model: case-only	N/A	-Virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 1, 3, 7 -Proportion of death, critical illness, and recovery	-Proportion of treatment-related adverse events	N/A	February 1, 2020/December 31, 2020	Anti-SARS-CoV-2 Inactivated Convalescent Plasma in the Treatment of COVID-19	Shanghai Public Health Clinical Center
Convalescent Plasma Collection and Treatment in Pediatrics and Adults	West Virginia University	Sequential assignment	N/A	-Plasma donor (time to identify eligible and willing donors, time for collection center to contact willing donors) -Plasma recipient (time from consent to infusion, survival)	-Plasma donor (time until plasma is donated) -Plasma recipient (treatment-emergent adverse events, morbidity reduction, reduced length of hospital stay, reduced length of stay on advanced respiratory support)	-Mild severity:standard of care -Moderate severity:convalescent plasma 1 unit -Severe or critical severity:convalescent plasma 2 units	April 16, 2020/March 30, 2021	Convalescent Plasma Collection and Treatment in Pediatrics and Adults	West Virginia University

Title of clinical trial	Sponsor	Intervention model	Study phase	Primary Outcomes	Secondary Outcomes	Study arms	Estimated start date/end date	Title of clinical trial	Sponsor

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