Message

From: Alexander, Paul (HHS/ASPA) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=BC4EDA8AD333439EB3D296AE0E0F9634-ALEXANDER,]
Sent: 8/19/2020 6:35:23 PM
To: Stephen Hahn [redacted] Shah, Anand (FDA/OC) [redacted] Caputo, Michael (HHS/ASPA) [redacted] Wagner, John (FDA/OC) [redacted]
Subject: All existing Convalescent plasma studies (2 reviews, 2 RCTs, 14 non randomized)
Attachments: Convalescent plasma summary table of existing studies as of August 19.doc

Hi Dr. Hahn and Anand, see this table as per our discussion today.

Michael and Wolf, this was the evidence I was referring to, it's the current 18 studies on Convalescent.

I wrote up a summary now quickly and my views...I did a risk of bias...as you see even the 2 RCTs have high risk of bias due to open label, underpower etc.

I share this to help give us cover in our decisions. It to me is well positioned. My view is that CP should be used and is showing to be safe, and an EUA as an example, if one is ever contemplated, is well credible and has merit. NIH has stepped out of their lane based on what I am reading now and I will tell you this, that nonrandomized evidence will shortly be mainstreamed alongside RCT evidence once it is high quality evidence.

Not because it is a RCT means it is optimal. Evidence based medicine is changing and I am part of the GRADE working group writing guidance on this. A well conducted nonrandomzied observational study (ideally prospective) that has large sample size, and has good multivariate adjustments, large magnitude of effect, a dose response relationship, and control for confounding etc. will TRUMP a poorly conducted RCT...pardon the pun.

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Sent: Wednesday, August 19, 2020 2:25 PM
To: Alexander, Paul (HHS/ASPA) [redacted]
Subject:

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Best,

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Dr. Paul Alexander
August 19th 2020

Convalescent Plasma (review of 18 studies; 2 reviews, 2 RCTs, 14 nonrandomized studies):

- At this time, the research on convalescent plasma (CP) is underpinned by largely small-sample size observational studies with small event number, and they are confounded mainly because of the lack of prognostic balance.
- One very large convenience sample (observational design) of 20,000 patients on adverse events adds important information to the possible use of CP in COVID-19 patients. The convenience sample appears to indicate that CP is generally safe and well tolerated in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.
- A Cochrane systematic-review found 20 studies (1 RCT, 3 controlled NRSIs, 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma. Researchers concluded there is great uncertainty on whether convalescent plasma is beneficial for people admitted to hospital with COVID-19.
- The RCT looked at CP (n=52 patients) vs standard treatment alone (n=51) with a median age of 70 and 58.3% of patients being male. Hypertension, cardiovascular disease, diabetes, kidney disease, and liver disease were the principle types of co-morbidities.
- The trial was stopped early before arriving at its targeting sample size of 200 suggestive that it was underpowered.
- Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the CP group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; $p = 0.03$); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the CP group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; $p = .83$) (P for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; $p = .30$) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; $p = .12$). CP treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; $p < .001$). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care.
- The RCT was open-label, randomization and concealment appeared reasonably well done. Methodologically an improvement from among the COVID-19 research published to date but not optimal methods wise.
- Larger sample sized RCTs are needed urgently to establish the benefit (or harm) of CP, and whether this treatment option will be stand-alone or work optimally in combination with other therapeutics.
- On balance, the preponderance of nonrandomized studies were small in size and methods not optimal but collectively, suggest that there is benefit and that CP is not harmful. The limited RCT evidence was not optimal methodologically and very small sample size. While evidence accumulates, CP should be used within ethically approved RCTs and off-label, as well as some form of EUA.

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CONVALESCENT PLASMA (CP)

There is insufficient evidence to draw a conclusion on benefits and harms.
The effectiveness is being evaluated in various randomized clinical trials.

OBSERVATIONAL (clinical)

[HYPERLINK "https:/doi.org/10.1001/jama.2020.4783"][25]; case-series; 2020	Convalescent plasma (CP) to all; 5; age range 36-73 years; 60% Note: CP administered to all between 10 and 22 days after admission	1 has hypertension and mitral insufficiency; antivirals (lopinavir/ritonavir; interferon alfa-1b; favipiravir; arbidol; darunavir) and corticosteroid methylprednisolone	Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA score decreased, and PAO2/FIO2 increased within 12 days (range, 172-278 before and 284-366 after). Viral loads also decreased and became negative within 12 days after the transfusion, and SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (range, 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients at 12 days after transfusion, and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Did not apply GRADE
[HYPERLINK "https://doi.org/10.1073/pnas.2004168117"][26]; case-series; 2020	CP to all; 10; median age was 52.5 years (IQR, 45.0–59.5); 60%	Hypertension 30%, cardiovascular and cerebrovascular disease 10%; arbidol, ribavirin, remdesivir, Interferon-α, oseltamivir, peramivir and corticosteroid methylprednisolone	Following transfusion, the level of neutralizing antibody quickly increased to 1:640 in five cases, and maintained at a high level (1:640) in remaining of cases. Researchers reported that the clinical symptoms were substantially improved. They also found an increase in oxyhemoglobin saturation within 3 days. Several parameters tended to improve as compared to pre-transfusion. Improved parameters included "increased lymphocyte counts and decreased C-reactive protein. Radiological examinations showed varying degrees of absorption of lung lesions within 7 days. The viral load was undetectable after transfusion in seven patients who had previous viremia". No severe adverse effects. Note: case-series, nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, not optimally comparative, sub-optimal reporting of methods and outcomes.	High; Did not apply GRADE
[HYPERLINK "https://doi.org/10.1016/j.chest.2020.03.039"][27]; case-series; 2020	CP to all; 4; 31, 55, 69, 73 years old and F, M, M, and pregnant F respectively	None reported; arbidol, lopinavir-ritonavir, ribavirin, interferon alpha inhalation, oseltamivir, albumin, zadaxin and immunoglobulin, antibacterial and antifungal drugs	Researchers reported no serious adverse reactions and all 4 patients recovered from COVID-19. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes. This early data is to be considered hypothesis generating, calling for well-designed randomised clinical studies.	High; Did not apply GRADE
[HYPERLINK "https://doi.org/10.1101/2020.04.07.20056440"][29]; case-series; 2020	CP to all three; 3; not reported; not reported	Not reported; not reported	There were 2 patients with negative conversions and 1 failure due to anaphylaxis shock (discontinued); 1st patient treated on 12th day admission, turned severe, 2nd treatment, then significantly improved (nucleic acid test became negative and symptoms improved) and met discharge criteria on 26th day, 2nd patient, treatment on 27th day, the nucleic acid test became negative 4 days later, 3rd patient was a 51-year old pregnant woman who suffered anaphylaxis shock and CP was discontinued).	High; Did not apply GRADE

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			Note: pre-print, small, only 3 patients, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, small events, not optimally comparative, sub-optimal reporting of methods and outcomes.	
[HYPERLINK "https://www.sciencedirect.com/science/article/pii/S0924857920301 31X?via%3Dihub"][48]; case-series; 2020	1 patient, 50-year old female	Antiviral therapy plus interferon-α2b, followed by lopinavir and ritonavir and empiric ceftriaxone	IVIG (20g) and thymalfasin were initiated, corticosteroid (intravenous 80 mg methylprednisolone) was also commenced and halved to 40mg two days later, symptoms deteriorated and ceftriaxone was replaced with piperacillin-tazobactam; initiated the administration of three consecutive sessions of PE with 6000ml plasma (frozen plasma served as the sole replacement solution) followed by 20g IVIG from DOI 14 to DOI 17; symptoms were almost all rapidly relieved, with three consecutive sessions of PE treatment; no adverse events or complications were seen during PE treatment; oxygenation index increased with oxygen saturation of 96%; patient was breathing ambient air oxygen and the blood pressure was re-established. Note: small case-series of n=1	High; Did not apply GRADE
[HYPERLINK "https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa228/5826985"][61]; retrospective observational; 2020	CP (n=6) vs no CP (15); 21; CP median 61.5 (31.5-77.8) vs control median 73 (60-79); 76%	Hypertension 19%, diabetes 28.5%, liver disease 9.5%, cardiovascular 4.7%, kidney 4.7%; antiviral treatment 76%, IVIG 90%, glucocorticoid pulse 76%. There was fever 85.7%, cough 90.5%, fatigue 67%, dyspnea 76%, bilateral pneumonia in 95%	There was respiratory failure in 100%, ARDS 85%, septic shock 52%, secondary infection 76%; 5 deaths in treatment (83%) vs 14 (93%) in control group, 100% SARS-CoV-2 clearance in treatment group vs in 4 patients (26.7%) in the control group and there was SARS-CoV-2 clearance before death in 5/5 fatal patients in treatment group vs 3/14 (21%) in control; the 6 treatment patients with respiratory failure received convalescent plasma at a median of 21.5 days after first detection of viral shedding; overall, it appears that CP treatment may halt SARS-CoV-2 shedding but failed in reducing mortality in critically end-stage COVID-19 patients; researchers suggested that treatment should be stated earlier. Note: nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, small sample size, a small number of events, sub-optimal reporting of methods and outcomes.	High; Very low certainty[1]
[HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/?term=Use+of+Convalescent+Plasma+Therapy+in+Two+COVID-19+Patients+with+Acute+Respiratory+Distress+Syndrome+in+Korea."][76]; observational case-series; 2020	CP; 2; ages 67 and 71; 1 males and 1 female	Both critical; a medical history of hypertension, previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): Concomitant therapy: 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empirical antibiotics, intubation and mechanical ventilator care, IV methylpred nisolone (0.5/1 mg/kg/day daily).	Both received lopinavir/ritonavir and hydroxychloroquine but showed persistent fever, rapidly aggravated hypoxemia and progressive bilateral infiltrations in accordance with the criteria of severe ARDS; following CP infusion, the patients showed improved oxygenation and chest X-rays with decreased inflammatory markers and viral loads; researchers reported that when used with systemic corticosteroids, there is the possibility of reducing excessive inflammatory response by corticosteroids as well as promoting the reduction of viral loads by convalescent plasma simultaneously. Note: small case series of 2 patients, not blinded for outcome detectors, not adjusted for confounding.	High; Did not apply GRADE
[HYPERLINK "https://www.medrxiv.org/c	5000 patients (of 8,932 enrolled patients with COVID-19) received CP; 5000; median age 62.3 (18.5,	72% respiratory failure, 63% dyspnea, 62% blood oxygen saturation ≤	81% patients had severe or life-threatening COVID-19 and 949 (19%) were judged to have a high risk of progressing to severe or life-threatening COVID-19; prior to COVID-19 convalescent plasma transfusion, a total of 3,316 patients (66%)	High; Did not apply GRADE

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ontent/10.1101/2020.05.12.20099879v1.full.pdf"] [78]; observational (retrospective case-series); 2020	97.8); 63.1% male	93%, 43% had lung infiltrates >50% within 24-28 hours of enrollment, 38% had a respiratory frequency ≥ 30 breaths·minute-1 , 34% had partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, 18% had multiple organ dysfunction or failure, and 15% had septic shock.	were admitted to the ICU; incidence of all serious adverse events (SAEs) in the first four hours after transfusion was <1%, Of the 36 reported SAEs, there were 25 reported incidences of related SAEs, including mortality (n=4), transfusion-associated circulatory overload (TACO; n=7), transfusion-related acute lung injury (TRALI; n=11), and severe allergic transfusion reactions (n=3); 2 (of 36) SAEs were judged as definitely related to the convalescent plasma transfusion by the treating physician. The seven-day mortality rate was 14.9%. Researchers suggested the CP is safe in a hospital setting to be used in COVID-19 and warrants further study. Note: large case-series, nonrandomized, confounded, optimal adjustments and steps such as stratification and masking not applied, not optimally comparative, sub-optimal reporting of methods and outcomes.	
[HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.05.20.20102236v1"] [88]; prospective case-control; 2020	CP transfused patients; 39; 55 ± 13; 64% males Note 1:4 matching 156; 1:2 matching 74	Asthma 8%, cancer 5%, CKD 3%, COPD 3%, diabetes 21%, obesity 54%; not reported	CP patients were more likely than control patients to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14, with an odds ratio of 0.86 (95% CI: 0.75~0.98; p=0.026). Plasma recipients also demonstrated improved survival, compared to control patients (log-rank test: p=0.032). In covariates-adjusted Cox model, convalescent plasma transfusion 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).	High; Very low certainty[1]
[HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/32473109/"] [93]; observational case-series; 2020	CP in patients with severe and/or life-threatening COVID-19 disease; 25; ages ranged from 19 to 77 years (median 51, interquartile range [IQR] 42.5 to 60); 44% male	40% diabetes, hypertension 32%, CKD 4%, hyperlipidemia 20%; hydroxychloroquine 100%, tocilizumab 56%, corticosteroids 36%, remdesivir 8%	At day 7 post-transfusion with CP, 9 (36%) patients had at least a 1-point improvement in clinical scale, and seven of those were discharged. By day 14 post-transfusion, 19 (76%) patients had at least a 1-point improvement in clinical status and 11 were discharged. No adverse events as a result of plasma transfusion were observed. Whole genome sequencing data did not identify a strain genotype-disease severity correlation. The data indicate that administration of convalescent plasma is a safe treatment option for those with severe COVID-19 disease. Note: small case series of 25 patients, not adjusted for confounding.	High; Did not apply GRADE
[HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.05.26.20113373v1.full.pdf"] [95]; one-arm multicenter interventional study; 2020	Hyperimmune plasma (CP); 46; mean age 63 years (SD 12); 61% male	Hypertension 46%, diabetes 17%, cardiovascular disease 14%, COPD 5%, CKD 9%, dyslipidemia 21%; antiviral 42%, antibiotics 84%, HCQ 86%, anticoagulant 98%	Twenty-four patients received one unit of plasma, 21 received two units and one patient received 3 units. Three patients (6.5%) died within 7 days (at 1, 4 and 6 days); two had important comorbidities, such as diabetes, hypertension and cancer, while the third had an extremely low PaO2/FiO2 level of 67 at the time of plasma infusion; among survivors, the severity of the condition at baseline was confirmed by the low oxygen saturation (mean 94%) and PaO2/FiO2 (mean 131); > than 89% of patients showed bilateral multilobe infiltrates at chest radiogram and all laboratory biomarkers were markedly elevated; at 7 days after plasma infusion PaO2/FiO2 increased by 112 units in survivors, the chest radiogram severity decreased in 23% of patients; CRP, Ferritin and LDH all decreased by 60, 36 and 20%, respectively; no or little improvement was present in the three deceased patients; five serious adverse events occurred in 4 patients. Note: nonrandomized, confounded, small case series of 46 patients, not optimally adjusted for confounding.	High; Very low certainty[1]
[HYPERLINK "https://mayoclinicproceedings.org/pb/as	Data from 28,000 patients including the initial 5,000[78] and subsequent 15,000 transfused patients. By June 2, 2020, a total of 20,000	NR clearly, NR clearly	The incidence of all serious adverse events was quite low; including transfusion reactions (n=89, <1%); thromboembolic or thrombotic events (n=87,1%); cardiac events (n=680, ~3%), notably, the vast majority of the thromboembolic or thrombotic events (n=55) and cardiac events (n=562) were	High; Very low certainty[1]

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sets/raw/Health%20Advance/journals/jmcp/jmcp_ft95_6_8.pdf"] [118]; observational convenience sample; 2020	patients had been transfused with COVID-19 convalescent plasma, thus, 7-day mortality data is presented for all 20,000 patients; 20,000; 7.6% 18-39 years, 31.8% 40-59 years, 27.1% 60-69%, 20.6% 70-79, 12.8% 80 and over; 60.8% males		judged to be unrelated to the plasma transfusion per se; the seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).	
[HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/32694043/"] [161]; observational; 2020	189 patients, 115 plasma, 74 control; mean age 56; 55.6% male	Hypertension 21.9%, diabetes 22.9%	Comparison of outcomes including all-cause mortality, total hospitalization days and patients' need for intubation between the two patient groups shows that total of 98 (98.2 %) of patients who received convalescent plasma were discharged from hospital which is substantially higher compared to 56 (78.7 %) patients in control group. Length of hospitalization days was significantly lower (9.54 days) in convalescent plasma group compared with that of control group (12.88 days). Only 8 patients (7%) in convalescent plasma group required intubation while that was 20 % in control group. Note: nonrandomized, selection bias is an issue and confounding bias, small sample size and events; control group comprised of mainly milder patients and also co-interventions with antivirals etc.	High; Very low certainty[1]
[HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.08.02.20166710v1.full.pdf"] [166]; observational case series; 2020	16 patients, case-series, all administered CP; age range 30-90; 68.7% males	Hypertension 25%, diabetes 19%, CHD 19%; NR	Among the 16 patients, 10 of them had a consistently positive result of viral NAA test before convalescent plasma transfusion. Eight patients (8/10) became negative from day 2 to day 8 after transfusion. Severe patients showed a shorter time for NAA test turning negative after transfusion (mean rank 2.17 vs 5.90, P = 0.036). Two critically ill patients transfused plasma with lower antibody level remained a positive result of NAA test. CRP level demonstrated a decline 1 day after convalescent plasma treatment, compared with the baseline (P = 0.017). No adverse events were observed during convalescent plasma transfusion. Note: case-series, small sample size, very provocative findings.	High; Very low certainty[1]
RCT (clinical)				
[HYPERLINK "https://jamanetwork.com/journals/jama/article-abstract/2766943?utm_campaign=articlePDF&utm_medium=articlePDFlink&utm_source=articlePDF&utm_content=jama.2020.10218"] [97]; RCT; 2020	CP added to standard treatment (n=52) vs standard treatment alone (n=51); 103; median age, 70 years s (IQR, 62-78 years); 58.3% male	Hypertension 54.3%, cardiovascular disease 25%, cerebrovascular 17.5%, diabetes 10.6%, kidney disease 5.8%, liver disease 10.7%	Among those with severe disease, the primary outcome occurred in 91.3% (21/23) of the convalescent plasma group vs 68.2% (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; *P* = .03); among those with life-threatening disease the primary outcome occurred in 20.7% (6/29) of the CP group vs 24.1% (7/29) of the control group (HR, 0.88 [95% CI, 0.30-2.63]; *P* = .83) (*P* for interaction = .17). There was no significant difference in 28-day mortality (15.7% vs 24.0%; OR, 0.65 [95% CI, 0.29-1.46]; *P* = .30) or time from randomization to discharge (51.0% vs 36.0% discharged by day 28; HR, 1.61 [95% CI, 0.88-2.93]; *P* = .12). CP treatment was associated with a negative conversion rate of viral PCR at 72 hours in 87.2% of the convalescent plasma group vs 37.5% of the control group (OR, 11.39 [95% CI, 3.91-33.18]; *P* < .001). Two patients in the CP group experienced adverse events within hours after transfusion that improved with supportive care. Researchers concluded that CP did not result in a statistically significant improvement in time to clinical improvement within 28 days, and no improvement in the risk of death. Note: the trial was terminated before it reached its targeted original sample size of 200 patients; only 103 were enrolled (for whom randomization was stratified by disease severity); the	High; Very low certainty[1]

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			study was underpowered and many comparisons between the CP group and the control group were not statistically significant; open-label, randomization and concealment appeared reasonably well done. Methodologically an improvement from among the COVID-19 research published to date.	
[HYPERLINK "https://www.medrxiv.org/content/10.1101/2020.07.01.20139857v1"] [138]; RCT; 2020	CP (ConvP); 85 enrolled when trial halted; median age 63 (IQR 56 – 74) years; 72% male	Diabetes 25.5%, hypertension 31.3%, cardiac 24.4%, pulmonary 33.7%, cancer 9.3%, kidney disease 8.7%; NR	The adjusted OR for overall mortality for patients treated with ConvP was 0.95 (CI 0.20 – 4.67., p=0.95). Of the 43 patients randomized to ConvP 6 (14%) had died while 11 of the 43 (26%) control patients had died. At that time, all 86 patients had been followed for at least 15 days after inclusion, and 75 and 32 for at least 30 and 60 days respectively. The trial was halted prematurely after 86 patients were enrolled. Although symptomatic for only 10 days (IQR 6-15) at the time of inclusion, 53 of 66 patients tested had anti-SARS-CoV-2 antibodies at baseline. A SARS-CoV-2 plaque reduction neutralization test showed neutralizing antibodies in 44 of the 56 (79%) patients tested with median titers comparable to the 115 donors (1:160 vs 1:160, p=0.40). These observations caused concerns about the potential benefit of convalescent plasma in the study population and after discussion with the data safety monitoring board the study was discontinued. No difference in mortality (p=0.95), hospital stay (p=0.68) or day-15 disease severity (p=0.58) was observed between plasma treated patients and patients on standard of care. Note: stopped early and unclear; randomization and concealment, blinding not optimally reported. Small sample size and events.	High; Very low certainty[1]
Systematic review				
[HYPERLINK "https://pubmed.ncbi.nlm.nih.gov/32648959/"] [149]; systematic-review; 2020	20 studies (1 RCT, 3 controlled NRSIs, 16 non-controlled NRSIs) with 5443 participants, of whom 5211 received convalescent plasma, and identified a further 98 ongoing studies evaluating convalescent plasma or hyperimmune immunoglobulin, of which 50 are randomised; hyperimmune immunoglobulin studies were found.	Not reported clearly; not reported clearly	4 controlled studies (1 RCT (stopped early) with 103 participants, of whom 52 received convalescent plasma; and 3 controlled NRSIs with 236 participants, of whom 55 received convalescent plasma) to assess effectiveness of convalescent plasma. Control groups received standard care at time of treatment without convalescent plasma. *All-cause mortality at hospital discharge (1 controlled NRSI, 21 participants);* very uncertain whether convalescent plasma has any effect on all-cause mortality at hospital discharge (risk ratio (RR) 0.89, 95% confidence interval (CI) 0.61 to 1.31; very low-certainty evidence). *Time to death (1 RCT, 103 participants; 1 controlled NRSI, 195 participants);* very uncertain whether convalescent plasma prolongs time to death (RCT: hazard ratio (HR) 0.74, 95% CI 0.30 to 1.82; controlled NRSI: HR 0.46, 95% CI 0.22 to 0.96; very low-certainty evidence). *Improvement of clinical symptoms, assessed by need for respiratory support (1 RCT, 103 participants; 1 controlled NRSI, 195 participants);* very uncertain whether convalescent plasma has any effect on improvement of clinical symptoms at seven days (RCT: RR 0.98, 95% CI 0.30 to 3.19), 14 days (RCT: RR 1.85, 95% CI 0.91 to 3.77; controlled NRSI: RR 1.08, 95% CI 0.91 to 1.29), and 28 days (RCT: RR 1.20, 95% CI 0.80 to 1.81; very low-certainty evidence). *Quality of life* No studies reported this outcome. Safety of convalescent plasma for people with COVID-19; 1 RCT, 3 controlled NRSIs and 10 non-controlled NRSIs assessing safety of convalescent plasma. Reporting of adverse events and serious adverse events was variable. The controlled studies reported on adverse events and serious adverse events only in participants receiving convalescent	AMSTAR II [7] critical appraisal of the review: high-quality

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			plasma. The duration of follow-up varied. Some, but not all, studies included death as a serious adverse event. *Grade 3 or 4 adverse events (13 studies, 201 participants)* The studies did not report the grade of adverse events. Thirteen studies (201 participants) reported on adverse events of possible grade 3 or 4 severity. The majority of these adverse events were allergic or respiratory events; very uncertain whether or not convalescent plasma therapy affects the risk of moderate to severe adverse events (very low-certainty evidence). *Serious adverse events (14 studies, 5201 participants)* Fourteen studies (5201 participants) reported on serious adverse events. The majority of participants were from one non-controlled NRSI (5000 participants), which reported only on serious adverse events limited to the first four hours after convalescent plasma transfusion. This study included death as a serious adverse event; they reported 15 deaths, four of which they classified as potentially, probably or definitely related to transfusion. Other serious adverse events reported in all studies were predominantly allergic or respiratory in nature, including anaphylaxis, transfusion-associated dyspnoea, and transfusion-related acute lung injury (TRALI); very uncertain whether or not convalescent plasma affects the number of serious adverse events. Researchers concluded there is great uncertainty on whether convalescent plasma is beneficial for people admitted to hospital with COVID-19.	
[HYPERLINK "url:%20https://www.medrxiv.org/content/10.1101/2020.07.29.20162917v1.full.pdf"] [165]; review; 2020	12 studies including three RCTs, five matched control studies, and four case series studies containing 804 COVID-19 patient outcomes; 804; mean or median age of patients enrolled in these studies ranged from 48 to 70 years, with a greater proportion of men than women in most studies (proportion of women: 25% to 56%).	NR; NR	All case-series studies demonstrated relatively low mortality rates for COVID-19 patients transfused with convalescent plasma (0% to 13%). Among RCTs, patients transfused with convalescent plasma exhibited a reduced mortality rate (13%) compared to non-transfused COVID-19 patients (26%; OR: 0.46, P = 0.03). Among matched control studies, patients transfused with convalescent plasma exhibited a reduced mortality rate (12%) compared to non-transfused COVID-19 patients (25%; OR: 0.41, P = 0.001). When patient outcomes from controlled studies were aggregated, patients transfused with convalescent plasma exhibited a reduced mortality rate (13%) compared to non-transfused COVID-19 patients (25%; OR: 0.43, P < 0.001). Meta-regression analysis indicated that mean or median cohort age, proportion of cohort receiving mechanical ventilation, and duration of study follow up did not affect the aggregate OR computed for all controlled studies (all coefficients P > 0.22). The fixed effect OR (OR: 0.44, P<0.001)	AMSTAR II [7] critical appraisal of the review: high-quality

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