expression and mutation signatures may provide the means of ultimately matching patients with treatments and matching treatment with response mechanisms. Given that relapsed disease appears to be chemoresistant across multiple classes of therapy, integration of personalized treatment is likely to be most effective when applied as early as possible.

References


Convalescent plasma for administration of passive antibodies against viral agents

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Administration of passive antibodies through transfusion of plasma from donors recovering from a viral infection has long been employed to treat individuals infected with the same pathogen. However, in studies with convalescent plasma (CP), differences and inherent limitations (e.g., sensitivity/specificity of tests to quantify neutralizing antibodies; sample size; scheduling of treatment [early/late CP administration vs. degree of disease severity]), the presence of confounders [concomitant treatments]), and restricted generalizability of data argued for large-scale, randomized, controlled trials.12 The results of a multicenter proof-of-concept, observational Italian study in 46 patients with moderate or severe acute respiratory distress syndrome due to infection with the novel coronavirus, SAR-CoV-2, who needed mechanical ventilation and/or continuous positive airway pressure are reported in this issue of the Journal.1 The interval between symptom onset and study inclusion was highly variable (2-29 days). The 7-day mortality rate was 6% in patients given CP compared with an expected 15% according to Italian statistics and 30% in a small concurrent cohort not treated with CP. Weaning from continuous positive airway pressure was achieved in 26 of 30 patients, and three of the seven intubated patients were extubated. Whether those who received CP earlier improved more or faster than patients who received plasma later in the course of the disease is not clarified, nor are the reasons for administering one, two or three CP bags provided. In this larger than previous uncontrolled reports, five serious adverse events (including 1 transfusion-related acute lung injury [TRALI]) occurred in four patients. Although TRALI may be triggered by transfused antibodies, CP was safe in this study as it was in
<table>
<thead>
<tr>
<th>Virus, Ref(s)</th>
<th>Design/Patients/Treatments/Objectives</th>
<th>Results/Interpretation/Limitations</th>
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<tr>
<td><strong>SARS-CoV-2</strong></td>
<td>JAMA 2020;323(16):1582-1589.</td>
<td>Following CP transfusion, body temperature normalized within 3 days (4/5 patients). Within 12 days, the SOFA score decreased; PaO₂/FiO₂ increased (range, 284-366 after vs. 172-276 before); viral loads became negative, and SARS-CoV-2-specific neutralizing antibody titers increased (range, 1:80-1:320 on day 7 vs. 1:40-1:160 before). ARDS resolved in 4 patients 12 days after CP transfusion, 3 patients stopped mechanical ventilation within 2 weeks of treatment. 3/5 patients were discharged from the hospital, 2 in a stable condition 37 days after CP.</td>
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**SARS-CoV-2** | Proc Natl Acad Sci U S A 2020; 117(17):9490-9496.  | By day 3 after CP transfusion, improved clinical symptoms and laboratory values, increases in neutralizing antibody titers, patients’ oxygen saturation and lymphocyte count; decreases in CRP, SARS-CoV-2 viral load, and radiological lung lesions (varying degrees of absorption of lung lesions within 7 days). No severe adverse events following CP administration.  |

**SARS-CoV-2** | Chest. 2020;158(1):e9-e13. | All recovered from the infection. Resolution or partial absorption of lung lesions (all cases); reduced viral load (2 cases), 3/4 discharged between days 18-43. Recovery/discharge within 1 to 4 weeks after starting CP transfusion; one patient discharged on supplemental oxygen, another required continued critical care for multi-organ failure. |

**SARS-CoV-2** | JAMA 2020;324(5):468-470.  | At the time of the termination, 103/200 patients (58.3% males, median age 70 years) had been enrolled. Of these, 98.1% (101/103) completed the trial. Within 28 days, clinical improvement was detected in 51.9% (73/141) in the CP group vs. 43.1% (23/54) in the control group (HR, 1.40 [95% CI: 0.79-2.49]; P=0.26). Among those with severe disease, improvement was found in 91.3% (21/23) of the CP group vs. 68.2% (15/22) in the control group (HR, 2.15 [95% CI: 1.07-4.32]; P=0.03). Among those with life-threatening disease, improvement was found in 29.1% (6/21) of the CP group vs. 24.1% (7/29) in the control group (HR, 1.88 [95% CI: 0.30-2.63]; P=0.83). At day 28, there was no difference in mortality (15.7% vs. 24.0%; OR, 0.65 [95% CI: 0.29-1.46]; P=0.30) or time to discharge (51.0% vs. 36.0%; HR, 1.61 [95% CI: 0.88-2.93]; P=0.12). CP treatment was associated with a higher conversion rate to negative viral PCR at 72 h (87.2% in the CP group vs. 37.5% in the control group (OR, 11.39 [95% CI: 3.91-33.18]; P<0.001). Two adverse events occurred in two patients in the CP group. |

**SARS-CoV-2** | Haematologica 2020;105(12):2834-2840. | Patients had been symptomatic for a mean of 14 days (SD, 7) and had had ARDS for a mean of 6 days (SD 3) prior to receiving CP. Three patients (6.5%) died within 7 days. Among survivors, PaO₂/FiO₂ increased by 112 units (95% CI: 82-142); severity of radiological signs decreased in 23% (95% CI: 5-42%); CRP, ferritin and lactate dehydrogenase levels decreased by 60%, 36% and 20%, respectively. Weaning from CPAP was achieved in 26/30 patients and 3/7 intubated patients could be extubated. Five serious adverse events occurred in four patients (1 TRALI), of which two were possibly treatment related. |

**Influenza A or B §** | Lancet Respir Med. 2019;7(11):941-950. | Randomized, double-blind phase III prospective trial. Patients of all ages with severe influenza A infection; onset of illness within 6 days of randomization. Randomization based on disease severity and age (< 18 yrs: >18 years): either two units (or pediatric equivalent) of high titer (≥1:80) or low titer (≥1:10) anti-influenza virus hemagglutinin antibodies; CP 28 days of follow-up. Objectives: efficacy of high-titer vs. low-titer CP. 9/238 randomized to the high-titer, 48/338 to the low-titer group. At baseline, 60% (43%) participants were in intensive care; 55/78 (71%) of participants were not in intensive care requiring oxygen. Early termination. No superiority of high-titer over low-titer plasma (OR on day 7: 1.22; 95% CI: 0.65-2.29, P=0.54). 34% of participants (47/138) experienced 88 serious adverse events, including ARDS. Ten patients died (6 [7%] in the high-titer group, 4 [9%] in the low-titer group, P=0.73), worsening of ARDS was the most common cause of death. |
156 received 500 mL of H-Ig, 152, placebo (224/508 influenza A serotypes and 84/308 influenza B serotypes). Clear rise in hemagglutination inhibition titers against influenza A; smaller rise in influenza B titers in the treated group. In subgroup analyses, the OR was 0.94 (0.55-1.59) in patients with influenza A and 3.19 (1.21-8.42) in those with influenza B (interaction P=0.023). Through 28 days of follow-up, 47/156 (30%) of patients in the H-Ig group and 65/152 (40%) in the placebo group died or experienced a serious adverse event (HR 1.10, 95% CI: 0.70-1.69; P=0.79).

Influenza A or B § §  

A prospective randomized controlled trial. Adults (≥18 years of age) in the H-Ig group and 45/152 (30%) in the placebo group died or transfused volumes.

Influenza A or B § §  

Randomized, double-blind, placebo-controlled trial. Adults (≥18 years of age), confirmed severe influenza A or B infection needing hospital treatment, symptoms starting within 7 days before randomization, assigned to standard care (which included antiviral therapy) + either 500 mL infusion of high-titer H-Ig (0.25 g/kg bodyweight, 24-75 g maximum) or saline placebo. Primary outcome: clinical status at day 7.

Influenza A (H1N1) **

Prospective cohort study. Within 7 days of symptom onset, 93 patients ≥18 years old with severe H1N1 2009 infection needing intensive care were given the possibility of a 500 mL CP infusion over a 4 h period (neutralizing antibody titer ≥1:160).

Influenza A (H1N1) **

Multicenter, prospective, double-blind, randomized controlled trial. Patients with severe H1N1 infection on standard antiviral treatment requiring intensive care and ventilatory support randomized to receive one dose of 0.4 g/kg of H-Ig (17 patients) or 0.4 g/kg normal intravenous immunoglobulins (18 matched patients) over a period of 4 h.

Ebola virus disease^^

Non-randomized, comparative study. Patients of various ages, confirmed EVD, two consecutive transfusions of 200 to 250 mL of ABO-compatible CP with varying levels of neutralizing antibodies. Transfusions initiated up to 2 days after diagnosis. Controls: 418 patients who had been treated at the same center during the previous 5 months. Primary outcome: risk of death from 3 to 16 days after diagnosis, adjustments for age: patients who died before day 3 excluded.

Ebola virus disease^^

Case series. Patients treated as those who did not receive 1 unit (450 mL) of ABO-compatible convalescent whole blood (CBW) within the first 24 h of admission over a period of 1-4 h.

SARS-CoV-1 **§§

Retrospective. 19 patients (38.7±12.39 years old) given 200-400 mL CP (coronavirus titer range 1:160-1:2560) compared to 21 patients (47.9±19.60 years old) given methylprednisolone pulses.

SARS-CoV-1 **§§

Retrospective. Patients (n=33/80) given CP (median volume 279 mL, coronavirus titer range 1:160-1:2560) within day 14 after the onset of symptoms versus patients given CP more than 14 days after hospital admission.

Discharge at the end of a 3-week hospitalization in 74% of subjects receiving CP and in 19% of those on methylprednisolone. Mortality: 0/19 (CP group) vs. 5/21 (steroid group). Unknown titer or type of antibodies affecting outcomes. Anti-SARS-CoV-1 antibodies contained within the CP not standardized.

For 3-week hospitalization, compared to the overall SARS-related mortality for admitted patients (17%, n=299), those receiving plasma earlier had a lower mortality rate (12.5%). No adverse events reported. No correlation between clinical response and antibody titers or transfused volumes.

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5,000 patients in another study. Also considering a risk/benefit analysis performed to improve the treatment of severe acute respiratory distress syndrome caused by SARS-CoV-2 infection, the Food and Drug Administration (FDA) issued guidance on CP collection and distribution in the USA and recommended conducting clinical trials with CP in the setting of SARS-CoV-2 infection. It has been proposed that, in such trials, one CP unit is used for post-exposure prophylaxis and one to two units for treatment of SARS-CoV-2 infection. For patients who fail to meet the criteria for enrollment in clinical trials, the FDA has approved protocols for emergency use and expanded access. In parallel, the plasma industry joined forces (the CoVlg-19 ALLIANCE) to increase plasma collection and prepare criteria for enrollment in clinical trials, the FDA has recommended conducting clinical trials with CP in the setting of SARS-CoV-2 infection. It has been proposed that, in such trials, one CP unit is used for post-exposure prophylaxis and one to two units for treatment of SARS-CoV-2 infection. For patients who fail to meet the criteria for enrollment in clinical trials, the FDA has approved protocols for emergency use and expanded access. In parallel, the plasma industry joined forces (the CoVlg-19 ALLIANCE) to increase plasma collection and produce safe and effective CP and hyperimmune immunoglobulins (H-Ig). Beside the USA, other countries...
are collecting CP to be used in SARS-CoV-2 infections, and many studies are ongoing.\(^7\) Parallel to the submission of the Italian study, an open-label, multicenter, randomized trial from China appeared, in which patients with SARS-CoV-2 and severe acute respiratory distress syndrome were randomized to 4-13 mL/kg of CP plus standard treatment vs. standard treatment alone (Table 1). The calculated sample size was 100 patients for each group. Due to the containment of the SARS-CoV-2 epidemic in China, the study was terminated when 103 of the 200 planned patients had been enrolled. At termination of the trial, improvement was found in 21/23 patients in the CP group vs. 15/22 in the control group (\(P=0.03\)) among those with severe disease, and in 6/29 of the CP group vs. 7/29 in the control group (\(P=0.83\)) among those with life-threatening disease. There was no between-group difference in mortality (\(P=0.30\)) and two adverse events were detected in two patients in the CP group.

While antibody administration by means of CP is indeed a reliable strategy for conferring immediate immunity against viral agents to individuals with SARS-CoV-2 infection, there is uncertainty about whether CP or H-Ig is the more effective product to be administered.\(^8,11\) While CP is characterized by donor-dependent variability in antibody specificity and titers, H-Ig contains standardized antibody concentrations. On the other hand, while the IgM fraction, a key weapon against some viruses, is removed from plasma during H-Ig fractionation, CP also provides coagulation factors (to fight hemorrhagic fevers, such as Ebola).\(^2\) Although specific antibodies hamper viral replication, the SARS-CoV spike (S) protein is the main antigenic component responsible for biological effects, e.g., host immune responses, neutralizing-antibody formation, T-cell responses and ultimately protective immunity.\(^10\) On the whole, the proportion of anti-S protein antibodies, relationships between IgG/IgA/IgM, standardization of antibody titers and optimal dosing and scheduling of CP administration are still major unknowns from studies conducted so far in the frame of the SARS-CoV-2 pandemic.

This scenario of growing interest from clinicians, patients, policy-makers, health systems and pharmaceutical industries provides an unprecedented opportunity to exert a major imprint on the practice of medicine.\(^2\) A concerted effort is warranted to achieve globally uniform, high-quality standards for CP or H-Ig preparations. In high-income countries, the industrial production of plasma-derived products has never been safer than nowadays both because of the guidelines produced by the FDA and European Medicines Agency on donor selection and screening and because of the availability of viral inactivation methods. Plasma is collected at plasmapheresis centers using technologies regularly inspected by governing bodies before approval for commercial use. Plasma is screened after each donation and re-screened in mini-pools for human immunodeficiency virus-1, hepatitis A, B and C viruses, and parvovirus B19, and Plasma Master Files are subject to yearly approval by regulatory agencies.\(^15\) Once collected, plasma from single donors may be administered directly to patients or pooled to manufacture plasma-derived products such as H-Ig, coagulation factors and others. The resulting products may be treated with solvent/detergent and/or super-heated (at 80° C for 3 days), pasteurized or nano-filtered. The aforementioned approaches are highly effective in minimizing pathogen transmission, as demonstrated by the fact that no blood-borne pathogen transmission has been reported since 1987 for commercially prepared plasma products received by patients with hemophilia, the epimrome of multi-transfused patients.\(^2\) In theory, however, risks remain pertaining to emerging and re-emerging pathogens (prions, non-lipid enveloped viruses) (Table 2), for which diagnosis and inactivation methods are still a challenge.\(^14\) The reasons for this caveat concerning risks include the lack of reliable screening tests for some pathogens (e.g., prions), no screening for unknown pathogens, and relative poor sensitivity/specificity of the available assay methods.\(^14\) Furthermore, some viral mutants may escape screening,\(^15\) which may also not pick up potential plasma contamination from infectious but not yet seropositive donors. In addition, there may be low-level chronic carriers among donors who remain undetected and yet contribute to infect the plasma pool.\(^17,18\) Finally, determining the prevalence of emerging pathogens may be difficult, whereas there is a long latency between infection and symptom onset.\(^19\)

On this background and with these knowledge gaps, the adaptation of screening methods is a constant challenge,\(^16\) and public health organizations and plasma pharmaceutical industries have combined efforts to tackle the risks. In the framework of its global perspective, the World Health Organization tries to minimize pathogen transmission through early information and public health vigilance on the emergence of regional pathogens capable of causing transfusion-transmitted infections (e.g., Zika virus in Brazil), even before local authorities manage to develop means to prevent blood-borne transmission.\(^20\) Because ‘zero risk’ in terms of product safety is unlikely, governing bodies provide guidance to identify factors relevant for pathogen transmission. As an example, the presence of blood-borne hepatitis E virus may pose significant threats to some people (e.g., the elderly, immunocompromised individuals) despite being of low risk to other potential recipients. Thus, in addition to the circumstances under which blood products are collected and manufactured, the nature of the pathogen (e.g., its physical characteristics, level of virulence, prevalence) and the patients’ characteristics (age, immune status, geographical location, lifestyle, treatment urgency) should be considered when choosing the individual treatment (and assessing an acceptable level of risk).

Alongside this scenario of basically satisfactory blood product safety in high-income countries, it should be considered that in most low/middle-income countries procedures for blood collection are seldom standardized, and donor selection, screening and viral inactivation often fail to meet the criteria validated and implemented by regulatory agencies in high-income countries. If insufficient anti-SARS-CoV-2 CP is available from high-income countries to meet global needs, the use of plasma from low/middle-income countries may become necessary but may also raise some issues, because the type and prevalence of infectious agents likely differ in different populations.\(^15\)

To sum up, if worldwide uniform advancements in blood-banking quality are encouraged in low/middle-income countries, there is now a global opportunity to perform clinical studies on the efficacy of CP or H-Ig in viral infections and address uncertainties on the occurrence of
serious adverse events related to the administration of these products. Removing regulatory barriers that limit the use of pathogen-reduction technology for CP collections would be a major help in this respect. The process of obtaining informed consent requires communication of risks and benefits of treatments to patients. SARS-CoV-2 is an easily inactivated enveloped virus, and strict regulations for plasma product manufacturing minimize the risk of known and unknown pathogens. Apart from emergency situations, the extent to which people should be further informed on specific risks associated with any particular product will depend on a variety of factors including availability of alternative treatments, and the patients’ characteristics (e.g., age, physical/mental condition, education/level of understanding, language barriers/religious beliefs). A good understanding by health care professionals of the sources and modes of production of plasma derivatives and of pathogen-reduction/inactivation techniques might be an additional benefit of studies involving CP.

Addendum
Parallel to the submission of this Editorial, a systematic review of completed (as of June 4, 2020) and ongoing (n=98) studies on the efficacy and safety of convalescent plasma or hyperimmune immunoglobulins to reduce mortality in patients with SARS-CoV-2 infection appeared (Cochrane Database Syst Rev. 2020;7(CD013600). Its provisional conclusions support the clinical relevance of the concepts summarized in the present report.

References