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Transfusion and Apheresis Sciences

The Clinical Trial Section Editorial

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Editorial

The transfer of immunity from a protected to an infected host dates back to the end of the XIXth century, on both experimental and clinical grounds. Perhaps the pioneer large scale experience has achieved during the so-called Spanish flu, a disease which killed almost twice to five times more people (depending on the model used) than the preceeding WWI. After that first experience, nearly all severe or serious infectious outbreaks involving a viral pathogen have been considered eligible for convalescent plasma collection from donors who have recovered from the infection [reviewed in: 1,2]; this therapy, however, was accompanied by all-time questions on the dose, the regimen, the amount of protective antibodies, the potential for deleterious effects, and the most appropriate stage of eligibility of recipients [3,4]. The question, in other words, remains as to how to protect against what: from the infection itself or from the severity of the infection?

Convalescent plasma treatment, i.e. passive polyclonal antibody administration to provide immediate immunity, has been used to improve the survival rate of patients with severe acute respiratory syndromes of viral etiology, as reviewed by Mair-Jenkins J et al. in their 2015 metanalysis [5]. Indeed, a number of convalescent plasma studies, unfortunately none

adequately controlled for bias, have reported positive outcomes, including decreased mortality in the so-called Spanish Influenza A (H1N1) infections in 1915-1917, the more recent Influenza A (H1N1)pdm09 infections in 2009/2010 as well SARS-CoV infections in 2003. On the contrary, convalescent plasma was found to provide no benefit for the treatment of Ebola disease [6] while being beneficial in the treatment of another hemorrhagic fever i.e. the Argentinian hemorrhagic fever [7].
Very early after the SARS-CoV-2 infection appeared to be potentially severe and lethal in a number of patients, most presenting with frailties, proposals were made to assess convalescent plasma therapy, either in compassionate situations or in randomized controlled trials (RCTs) [8-10]. Two paramount questions were to be addressed prior to promoting such a treatment: firstl, to assess whether the recovering person was capable to raise sustainable amounts of antibodies to be collected by plasmapheresis; and secondly, whether antibodies were indeed neutralizing and not facilitating (such as in certain viral infections, the most exemplary being Dengue viruses, against the other three serotypes) [3,11].

At a speed never seen so far, robust data accumulated regarding the complexity of antibodies made against SARS-CoV-2 moieties (the virus signature track) or by COVID-19 suffering patients, not necessarily overlapping. Indeed, while COVID-19 healers were proven to raise significant amounts of antibodies that do not vanish immediately and last for weeks and likely months [12,13], pathogenic antibodies were also made in parallel. These can bind to macrophages and cause acute lung injury [14], damage vascular endothelium leading to endotheliopathy [15] and possibly coagulopathy [16], and dampen antiviral natural defense when directed to type I interferons [17]. It has been shown that—not unlikely as several other infections, such as HIV and others—the SARS-CoV-2 virus alters the germinal center and forces extrafollicular antibody making [18,19]. In spite of this, recent evidence indicates that robust antibody protection persists for months [20,21], and, if any, enhancing or facilitating antibodies were of moderate concentration.

Collection of convalescent plasma preceded accumulation of scientific evidence that antibodies were neutralizing and not enhancing, and in a quantity large enough to mediate protection, demonstrating that an unprecedented race was engaged against the pandemic,

barely allowing time to discuss ethical issues [22,23], with the objective to learn as much as possible to justify the strongly wished vaccine approach.

Less than a single year after the initial reports of the severity of the disease, knowledge has accumulated regarding the potential of convalescent plasma: encouraging data were presented after 3 months of inclusion in a large series of recipients by Joyner et al. [24]. Next, Li et al [25] concluded that: "Among patients with severe or life-threatening COVID-19, convalescent plasma therapy added to standard treatment did not significantly improve the time to clinical improvement within 28 days, although the trial was terminated early and may have been underpowered to detect a clinically important difference". In contrast, Liu et al found that their retrospective, propensity score–matched case–controlled study assessed the effectiveness of convalescent plasma therapy with less oxygen requirements on day 14 after transfusion and less worsened cases in plasma recipients compared to propensity score–matched controls [26]. Salazar et al reported a significant reduction ($P = 0.047$) in mortality within 28 days, specifically in patients transfused within 72 hours of admission with plasma with an anti-spike protein receptor binding domain titer of ≥1:1350, and suggested that that treatment of COVID-19 with high anti–receptor binding domain IgG titer convalescent plasma is efficacious in early-disease patients [27]. Agarwal et al, however, found that convalescent plasma was not associated with a reduction of progression to disease or all cause of mortality [28]. In aggregate, Joyner et al, having compiled (nearly) all submitted data—not necessarily peer-reviewed as many are loaded on the MedRXiv site—concluded in favor of a protective effect of convalescent plasma [30]. More recently, convalescent plasma was found to be not superior to placebo in a randomized trial involving hospitalized patients with COVID-19 pneumonia [29]. Apparent discrepancies in conclusions may well be the result of certain inconsistency in defining patient groups (severity, time-course of infection, and outcomes), as was observed in other main trials addressing controversies in blood transfusion; the same concerns were for e.g. raised in this Journal à propos the age of blood [31]. These types of inconsistencies are, in general, pondered in metanalyses. It remained to confirm that transfusion of convalescent plasma was safe, which Joyner reviewed in 5,000 transfused COVID-19 patients [30]. Nguyen et al reviewed, in detail, the adverse reactions in 427 patients having received convalescent plasma and did not report increased risks compared to anticipated side effects [32]. Of note, the observed

reaction rate was 12.9%, among which 82% (mainly fever, hypoxia or both) were attributed to the underlying disease.

Interestingly, convalescent plasma therapy has proven to be beneficial in B-cell depleted patients having protracted COVID-19 [33], with an acknowledged limit inherent to uncontrolled observations [34]. Compassionate plasma therapy was applied early in the disease course [35-37]. As many more RCTs or compassionate programs are run in major healthcare facilities or within international consortiums, regulatory bodies—such as the FDA—also made more precise recommendations [38].

Very recently, investigators have reported (in a not-yet peer-reviewed format) positive results regarding the very early (within 72 hours of mild COVID-19 symptoms) transfusion of convalescent plasma in patients over 75 years old [39]. In this randomized study, convalescent plasma transfusion was associated with significant reduction in the occurrence of severe respiratory disease. These findings, reminiscent of recently reported findings with an anti-SARS-Cov-2 monoclonal treatment [40] as well as much older findings with convalescent plasma treatment of the Argentinian hemorrhagic fever [41], highlight the importance of early intervention when considering passive immunotherapy to treat infectious diseases. As we now move into the COVID-19 vaccination era, passive immunotherapy may become an important early therapeutic intervention for those poorly responding to vaccination (such as patients with acquired immunodeficiency, and possibly the elderly).

In conclusion, convalescent plasma therapy remains a solid option to treat COVID patients, though this option falls into a portfolio of many other therapeutic approaches and does not provide complete cure. The treatment schedule is likely to be refined to sort out the target populations and the most appropriate time frame, and also when to collect plasma from convalescent donors [42]. With a broader perspective, it is interesting to note that once more (after e.g. the Ebola virus saga) plasma therapy competes with vaccine development, the former being not completely disregarded when the latter comes into reality as antibody-enriched plasma may well be obtained from vaccinated persons, to prepare purified, neutralizing antibodies as also recommended by the FDA [43]. Two sets of conclusions can

be temporarily drawn at this time. First, this pandemic has revealed how fragile the combination of healthcare and economy, forcing to state decisions that altered autonomy of populations and individual freedom. The swiftness of incremental health care measures to handle actual patients and to protect the rest of the population is barely compatible with the necessary in-depth ethical analysis of all situations and consequences. Secondly, there is an urgent need to set up—in forthcoming preparedness plans for the next pandemic (as this seems to be inevitable)—clearer outcomes to measure, in order to allow for the best-fitted clinical trials. Methods and ethics are more than ever paramount to accompany the vortex of medical and scientific achievements under pressure such as seen in this SARS-CoV-2 crisis.

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References

1. Garraud O, Heshmati F, Pozzetto B, Lefrere F, Girot R, Saillol A, Laperche S. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. Transfus Clin Biol 2016;23:39-44
2. Wong HK, Lee CK. Pivotal role of convalescent plasma in managing emerging infectious diseases. Vox Sang 2020;115:545-547
3. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130:1545-1548
4. Garraud O. Passive immunotherapy with convalescent plasma against COVID-19? What about the evidence base and clinical trials? Transfus Apher Sci 2020;59:102858
5. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw FM, Lim WS, Makki S, Rooney KD, Nguyen-Van-Tam JS, Beck CR; Convalescent Plasma Study Group. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211:80-90

6. van Griensven, J., Edwards, T., de Lamballerie, X., Semple, M. G., Gallian, P., Baize, S., Horby, P. W., Raoul, H., Magassouba, N., Antierens, A., Lomas, C., Faye, O., Sall, A. A., Fransen, K., Buyze, J., Ravinetto, R., Tiberghien, P., Claeys, Y., De Crop, M., Lynen, L., … Ebola-Tx Consortium (2016). Evaluation of Convalescent Plasma for Ebola Virus Disease in Guinea. New Eng J Med;374:33–42
7. Ruggiero HA, Pérez Isquierdo F, Milani HA, Barri A, Val A, Maglio F, Astarloa L, Gonzalez Cambaceres C, Milani HL, Tallone JC. Traitement de la fièvre hémorragique argentine par le plasma de convalescent : 4,433 cas [Treatment of Argentine hemorrhagic fever with convalescent's plasma. 4433 cases]. Presse Med 1987;55:2239-2342
8. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, Wang F, Li D, Yang M, Xing L, Wei J, Xiao H, Yang Y, Qu J, Qing L, Chen L, Xu Z, Peng L, Li Y, Zheng H, Chen F, Huang K, Jiang Y, Liu D, Zhang Z, Liu Y, Liu L. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA 2020;323:1582-1589
9. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, van Buskirk C, Grossman BJ, Joyner M, Henderson JP, Pekosz A, Lau B, Wesolowski A, Katz L, Shan H, Auwaerter PG, Thomas D, Sullivan DJ, Paneth N, Gehrie E, Spitalnik S, Hod EA, Pollack L, Nicholson WT, Pirofski LA, Bailey JA, Tobian AA. Deployment of convalescent plasma for the prevention and treatment of COVID-19. J Clin Invest 2020;130:2757-2765
10. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, Zhou M, Chen L, Meng S, Hu Y, Peng C, Yuan M, Huang J, Wang Z, Yu J, Gao X, Wang D, Yu X, Li L, Zhang J, Wu X, Li B, Xu Y, Chen W, Peng Y, Hu Y, Lin L, Liu X, Huang S, Zhou Z, Zhang L, Wang Y, Zhang Z, Deng K, Xia Z, Gong Q, Zhang W, Zheng X, Liu Y, Yang H, Zhou D, Yu D, Hou J, Shi Z, Chen S, Chen Z, Zhang X, Yang X. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci USA 2020;117:9490-9496
11. Lee WS, Wheatley AK, Kent SJ, DeKovsky BJ Antibody-dependent enhancement and SARS-CoV-2 vaccines and therapies. Nat Microbiol 2020;5;1185–1191
12. Chen Y, Zuiani A, Fischinger S, Mullur J, Atyeo C, Travers M, Lelis FJN, Pullen KM, Martin H, Tong P, Gautam A, Habibi S, Bensko J, Gakpo D, Feldman J, Hauser BM, Caradonna TM, Cai Y, Burke JS, Lin J, Lederer JA, Lam EC, Lavine CL, Seaman MS, Chen B, Schmidt AG, Balazs AB, Lauffenburger DA, Alter G, Wesemann DR. Quick COVID-19

Healers Sustain Anti-SARS-CoV-2 Antibody Production. Cell 2020;S0092-8674(20)31458-6. doi: 10.1016/j.cell.2020.10.051

13. Atyeo C, Fischinger S, Zohar T, Slein MD, Burke J, Loos C, McCulloch DJ, Newman KL, Wolf C, Yu J, Shuey K, Feldman J, Hauser BM, Caradonna T, Schmidt AG, Suscovich TJ, Linde C, Cai Y, Barouch D, Ryan ET, Charles RC, Lauffenburger D, Chu H, Alter G. Distinct Early Serological Signatures Track with SARS-CoV-2 Survival. Immunity 2020;53:524-532.e4
14. Liu L, Wei Q, Lin Q, Fang J, Wang H, Kwok H, Tang H, Nishiura K, Peng J, Tan Z, Wu T, Cheung KW, Chan KH, Alvarez X, Qin C, Lackner A, Perlman S, Yuen KY, Chen Z. Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection. JCI Insight 2019;4:e123158
15. Rauch A, Dupont A, Goutay J, Caplan M, Staessens S, Moussa M, Jeanpierre E, Corseaux D, Lefevre G, Lassalle F, Faure K, Lambert M, Duhamel A, Labreuche J, Garrigue D, De Meyer SF, Staels B, Van Belle E, Vincent F, Kipnis E, Lenting PJ, Poissy J, Susen S; Lille COVID Research Network (LICORNE); Members of the LICORNE Scientific Committee. Endotheliopathy Is Induced by Plasma From Critically Ill Patients and Associated With Organ Failure in Severe COVID-19. Circulation 2020;142:1881-1884
16. Zuo Y, Estes SK, Ali RA, Gandhi AA, Yalavarthi S, Shi H, Sule G, Gockman K, Madison JA, Zuo M, Yadav V, Wang J, Woodard W, Lezak SP, Lugogo NL, Smith SA, Morrissey JH, Kanthi Y, Knight JS. Prothrombotic autoantibodies in serum from patients hospitalized with COVID-19. Sci Transl Med 2020;12:eabd3876
17. Bastard P, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Béziat V, Manry J, Shaw E, Haljasmägi L, Peterson P, Lorenzo L, Bizien L, Trouillet-Assant S, Dobbs K, de Jesus AA, Belot A, Kallaste A, Catherinot E, Tandjaoui-Lambiotte Y, Le Pen J, Kerner G, Bigio B, Seeleuthner Y, Yang R, Bolze A, Spaan AN, Delmonte OM, Abers MS, Aiuti A, Casari G, Lampasona V, Piemonti L, Ciceri F, Bilguvar K, Lifton RP, Vasse M, Smadja DM, Migaud M, Hadjadj J, Terrier B, Duffy D, Quintana-Murci L, van de Beek D, Roussel L, Vinh DC, Tangye SG, Haerynck F, Dalmau D, Martinez-Picado J, Brodin P, Nussenzweig MC, Boisson-Dupuis S, Rodríguez-Gallego C, Vogt G, Mogensen TH, Oler AJ, Gu J, Burbelo PD, Cohen JI, Biondi A, Bettini LR, D'Angio M, Bonfanti P, Rossignol P, Mayaux J, Rieux-Laucat F,

Husebye ES, Fusco F, Ursini MV, Imberti L, Sottini A, Paghera S, Quiros-Roldan E, Rossi C, Castagnoli R, Montagna D, Licari A, Marseglia GL, Duval X, Ghosn J; HGID Lab; NIAID-USUHS Immune Response to COVID Group; COVID Clinicians; COVID-STORM Clinicians; Imagine COVID Group; French COVID Cohort Study Group; Milieu Intérieur Consortium; CoV-Contact Cohort; Amsterdam UMC Covid-19 Biobank; COVID Human Genetic Effort, Tsang JS, Goldbach-Mansky R, Kisand K, Lionakis MS, Puel A, Zhang SY, Holland SM, Gorochov G, Jouanguy E, Rice CM, Cobat A, Notarangelo LD, Abel L, Su HC, Casanova JL. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020;370:eabd4585

18. Kaneko N, Kuo HH, Boucau J, Farmer JR, Allard-Chamard H, Mahajan VS, Piechocka-Trocha A, Lefteri K, Osborn M, Bals J, Bartsch YC, Bonheur N, Caradonna TM, Chevalier J, Chowdhury F, Diefenbach TJ, Einkauf K, Fallon J, Feldman J, Finn KK, Garcia-Broncano P, Hartana CA, Hauser BM, Jiang C, Kaplonek P, Karpell M, Koscher EC, Lian X, Liu H, Liu J, Ly NL, Michell AR, Rassadkina Y, Seiger K, Sessa L, Shin S, Singh N, Sun W, Sun X, Ticheli HJ, Waring MT, Zhu AL, Alter G, Li JZ, Lingwood D, Schmidt AG, Lichterfeld M, Walker BD, Yu XG, Padera RF Jr, Pillai S; Massachusetts Consortium on Pathogen Readiness Specimen Working Group. Loss of Bcl-6-Expressing T Follicular Helper Cells and Germinal Centers in COVID-19. Cell 2020;183:143-157.e13
19. Woodruff MC, Ramonell RP, Nguyen DC, Cashman KS, Saini AS, Haddad NS, Ley AM, Kyu S, Howell JC, Ozturk T, Lee S, Suryadevara N, Case JB, Bugrovsky R, Chen W, Estrada J, Morrison-Porter A, Derrico A, Anam FA, Sharma M, Wu HM, Le SN, Jenks SA, Tipton CM, Staitieh B, Daiss JL, Ghosn E, Diamond MS, Carnahan RH, Crowe JE Jr, Hu WT, Lee FE, Sanz I. Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. Nat Immunol 2020;21:1506-1516
20. Wajnberg A, Amanat F, Firpo A, Altman DR, Bailey MJ, Mansour M, McMahon M, Meade P, Mendu DR, Muellers K, Stadlbauer D, Stone K, Strohmeier S, Simon V, Aberg J, Reich DL, Krammer F, Cordon-Cardo C. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. Science 2020:eabd7728
21. Iyer AS, Jones FK, Nodoushani A, Kelly M, Becker M, Slater D, Mills R, Teng E, Kamruzzaman M, Garcia-Beltran WF, Astudillo M, Yang D, Miller TE, Oliver E, Fischinger S, Atyeo C, Iafrate AJ, Calderwood SB, Lauer SA, Yu J, Li Z, Feldman J, Hauser BM, Caradonna TM, Branda JA, Turbett SE, LaRocque RC, Mellon G, Barouch

DH, Schmidt AG, Azman AS, Alter G, Ryan ET, Harris JB, Charles RC. Persistence and decay of human antibody responses to the receptor binding domain of SARS-CoV-2 spike protein in COVID-19 patients. Sci Immunol 2020;5:eabe0367

22. Garraud O. COVID-19, transfusion, and publishing ethics. Transfus Clin Biol 2020;27:201-202
23. Barroga E, Matanguihan GJ. Fundamental Shifts in Research, Ethics and Peer Review in the Era of the COVID-19 Pandemic. J Korean Med Sci 2020;35:e395
24. Joyner MJ, Senefeld JW, Klassen SA, Mills JR, Johnson PW, Theel ES, Wiggins CC, Bruno KA, Klompas AM, Lesser ER, Kunze KL, Sexton MA, Diaz Soto JC, Baker SE, Shepherd JRA, van Helmond N, van Buskirk CM, Winters JL, Stubbs JR, Rea RF, Hodge DO, Herasevich V, Whelan ER, Clayburn AJ, Larson KF, Ripoll JG, Andersen KJ, Buras MR, Vogt MNP, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Paneth NS, Fairweather D, Wright RS, Carter RE, Casadevall A. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience. medRxiv [Preprint]. 2020.08.12.20169359
25. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA. 2020;324:460–470
26. Liu STH, Lin HM, Baine I. Wajnberg A, Gumprecht JP, Rahman F, Rodriguez D, Tandon P, Bassily-Marcus A, Bander J, Sanky Cn Dupper A, Zheng A, Nguyen FT, Amanat F, Stabbauer D, Altman DR, Chen BK, Krammer F, Rao Mendu D, Firpo-BConvalescent plasma treatment of severe COVID-19: a propensity score–matched control study. Nat Med 2020;26;1708–1713
27. Salazar E, Christensen PA, Graviss EA, Nguyen DT, Castillo B, Chen J, Lopez BV, Eagar TN, Yi X, Zhao P, Rogers J, Shehabeldin A, Joseph D, Masud F, Leveque C, Olsen RJ, Bernard DW, Gollihar J, Musser JM. Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti-Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG. Am J Pathol 2020:S0002-9440(20)30489-2
28. Agarwal A, Mukherjee A, Kumar G, Chatterjee P, Bhatnagar T, Malhotra P; PLACID Trial Collaborators. Convalescent plasma in the management of moderate covid-19 in

adults in India: open label phase II multicentre randomised controlled trial (PLACID Trial). BMJ 2020;371:m3939. Erratum in: BMJ 2020;371:m4232

29. Simonovich VA, Burgos Pratx LD, Scibona P, Beruto MV, Vallone MG, Vazquez C, Savoy N, Giunta DH, Perez LG, del Sanchez M, Gamarnik AV, Ojeda DS, et al, for the PlasmaR study group. A ranndomized trial of convalescent plasma in Covid-19 penumonia. N Eng J Med 2020; DOI: 10.1056/NEJMoa2031304
30. Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompas AM, Wiggins CC, Shepherd JR, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MN, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Van Buskirk CM, Winters JL, Stubbs JR, Paneth NS, Verdun NC, Marks P, Casadevall A. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest 2020;130:4791-4797
31. Garraud O. Clinical trials in Transfusion Medicine and hemotherapy: Worth moving forward in evaluating 'fresh' versus 'old' blood cell components? Transfus Apher Sci 2017;56:98-99
32. Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, Carter RE, Klompas AM, Wiggins CC, Shepherd JR, Rea RF, Whelan ER, Clayburn AJ, Spiegel MR, Johnson PW, Lesser ER, Baker SE, Larson KF, Ripoll JG, Andersen KJ, Hodge DO, Kunze KL, Buras MR, Vogt MN, Herasevich V, Dennis JJ, Regimbal RJ, Bauer PR, Blair JE, Van Buskirk CM, Winters JL, Stubbs JR, Paneth NS, Verdun NC, Marks P, Casadevall A. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest 2020;130:4791-4797
33. Nguyen, FT, van den Akker, T, Lally, K, et al. Transfusion reactions associated with COVID-19 convalescent plasma therapy for SARS-CoV-2. Transfusion 2020;1–16. https://doi.org/10.1111/trf.16177
34. Hueso T, Pouderoux C, Péré H, Beaumont AL, Raillon LA, Ader F, Chatenoud L, Eshagh D, Szwebel TA, Martinot M, Camou F, Crickx E, Michel M, Mahevas M, Boutboul D, Azoulay E, Joseph A, Hermine O, Rouzaud C, Faguer S, Petua P, Pommeret F, Clerc S, Planquette B, Merabet F, London J, Zeller V, Ghez D, Veyer D, Ouedrani A, Gallian P, Pacanowski J, Mékinian A, Garnier M, Pirenne F, Tiberghien P, Lacombe K.

Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. Blood 2020;136:2290-2295

35. Murphy MF, Dzik S. COVID-19, plasma, and hypogammaglobulinemia. Blood 2020;136:2245-2246
36. Sabando Vélez BE, Plaza Meneses C, Felix M, Vanegas E, Mata VL, Romero Castillo H, Oliveros Alvear JW, Boloña E, Alejandra Posligua M, Layedra Bardi LR, Vera Paz C, Cherrez-Ojeda I. A practical approach for the compassionate use of convalescent plasma in patients with severe COVID-19 in developing countries. J Infect Dev Ctries 2020;14:737-741
37. Maor Y, Cohen D, Paran N, Israely T, Ezra V, Axelrod O, Shinar E, Izak M, Rahav G, Rahimi-Levene N, Bazofin BM, Gelman R, Dicker D, Brosh-Nissimov T, Megged O, Dahan D, Benov A, Paz A, Edward K, Moran A, Rogowski O, Sorkine P, Mayo A, Zimhony O, Chen J. Compassionate use of convalescent plasma for treatment of moderate and severe pneumonia in COVID-19 patients and association with IgG antibody levels in donated plasma. EClinicalMedicine 2020;26:100525
38. Vlachogianni G, Hassapopoulou-Matamis H, Politis C, Fylaki E, Mentis A. A case of COVID-19 Convalescent Plasma Donation in Greece: Directed donation for compassionate use in the donor's critically ill father. Transfus Clin Biol 2020;27:269-270
39. FDA, 2020. https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
40. Libster R, Pérez Matrc G, Wappner D, et al. Prevention of severe COVID-19 in the elderly by early high titer plasma. MedRxiv, posted November 13th, 2020, https://doi.org/10.1101/2020.11.20.20234013doi
41. Enria DA, Maiztegui JI. Antiviral treatment of Argentine hemorrhagic fever.Antiviral Res. 1994;23:23-31
42. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Adams AC, Van Naarden J, Custer KL, Shen L, Durante M, Oakley G, Schade AE, Sabo J, Patel DR, Klekotka P, Skovronsky DM; BLAZE-1 Investigators. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med 2020:NEJMoa2029849

43. Tiberghien P, de Lamballerie X, Morel P, Gallian P, Lacombe K, Yazdanpanah Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how? Vox Sang 2020;115:488-494
44. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, Huhn G, Cardona J, Mocherla B, Stosor V, Shawa I, Adams AC, Van Naarden J, Custer KL, Shen L, Durante M, Oakley G, Schade AE, Sabo J, Patel DR, Klekotka P, Skovronsky DM; BLAZE-1 Investigators. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. N Engl J Med. 2020:NEJMoa2029849
45. FDA, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19