Urban M. Fietzek, M.D.
Ludwig-Maximilians-University Hospital
Munich, Germany
urban.fietzek@med.uni-muenchen.de

Philip Albrecht, M.D.
University Hospital of Düsseldorf
Düsseldorf, Germany

Tobias Bäumer, M.D.
University of Lübeck
Lübeck, Germany

Drs. Fietzek, Albrecht, and Bäumer report being chairpersons of the German Workgroup Botulinum Toxin (Arbeitskreis Botulinumtoxin) of the German Neurologic Society (Deutsche Gesellschaft für Neurologie). Dr. Fietzek reports receiving research funds from the German Foundation for Neurology, honoraria from Ipsen Pharma and Allergan–AbbVie for educational work, consulting fees from Modag, and travel funds from Orbit Health. Dr. Albrecht reports receiving research funds from Deutsche Forschungsgemeinschaft and the European Regional Development Fund; research grants, travel funds, and speaker's fees from AbbVie, Biogen, Celgene–Bristol Myers Squibb, Ipsen Pharma, Merck, Merz Therapeutics, Novartis, and Roche; and speaker's fees from Janssen Cilag, Eli Lilly, Pfizer, Sandoz, Sanofi, and Teva Pharmaceuticals. Dr. Bäumer reports receiving a grant from the German Research Foundation, speaker's fees and consulting fees from Pelzerhaken Children's Center, and speaker's fees, consulting fees, and research funds from Allergan–Abbvie, Ipsen Pharma, and Merz Therapeutics. No other potential conflict of interest relevant to this letter was reported.

1. Marques A, Pereira B, Simonetta-Moreau M, et al. Trial of botulinum toxin for isolated or essential head tremor. N Engl J Med 2023;389:1753-65.
2. Kreisler A, Gerrebout C, Defebvre L, Demondion X. Accuracy of non-guided versus ultrasound-guided injections in cervical muscles: a cadaver study. J Neurol 2021;268:1894-902.
3. Ko YD, Yun SI, Ryoo D, Chung ME, Park J. Accuracy of ultrasound-guided and non-guided botulinum toxin injection into neck muscles involved in cervical dystonia: a cadaveric study. Ann Rehabil Med 2020;44:370-7.
4. Schramm A, Huber D, Möbius C, Münchau A, Kohl Z, Bäumer T. Involvement of obliquus capitis inferior muscle in dystonic head tremor. Parkinsonism Relat Disord 2017;44:119-23.

DOI: 10.1056/NEJMc2314018

THE AUTHORS REPLY: We agree with Fietzek et al. that ultrasonographically guided injections of botulinum toxin have theoretical advantages over electromyographically guided injections, including insight about the exact anatomical location of injected muscles.[1] Although the potential relevance of ultrasonographically guided injections has been extensively described,[2] evidence-based studies are rare.[3,4] A systematic review assessing the effect of different injection-guiding techniques on the effectiveness of botulinum toxin therapy concluded that no specific recommendations could be made regarding the choice of instrumented guiding technique.[3] Furthermore, a study comparing nonguided injections with ultrasonographically guided injections showed no between-group difference with regard to a reduction in the severity of cervical dystonia or with regard to adverse events,[5] probably owing to the diffusivity of botulinum toxin. Further randomized, controlled trials are needed to provide clear recommendations on the guiding technique to inform future research and clinical practice. Nevertheless, ultrasonographic guidance may help in understanding which muscles are predominantly involved in isolated or essential head tremor subtypes (no–no and yes–yes movements or mixed tremor) and may help to personalize such injections.

Ana Marques, M.D., Ph.D.
Isabelle Rieu, Ph.D.
Franck Durif, M.D., Ph.D.
Centre Hospitalier Universitaire Clermont-Ferrand
Clermont-Ferrand, France
ar_marques@chu-clermontferrand.fr

Since publication of the article, the authors report no further potential conflict of interest.

1. Kreisler A, Gerrebout C, Defebvre L, Demondion X. Accuracy of non-guided versus ultrasound-guided injections in cervical muscles: a cadaver study. J Neurol 2021;268:1894-902.
2. Hong JS, Sathe GG, Niyonkuru C, Munin MC. Elimination of dysphagia using ultrasound guidance for botulinum toxin injections in cervical dystonia. Muscle Nerve 2012;46:535-9.
3. Grigoriu A-I, Dinomais M, Rémy-Néris O, Brochard S. Impact of injection-guiding techniques on the effectiveness of botulinum toxin for the treatment of focal spasticity and dystonia: a systematic review. Arch Phys Med Rehabil 2015;96(11):2067-78.e1.
4. Rodrigues FB, Duarte GS, Marques RE, et al. Botulinum toxin type A therapy for cervical dystonia. Cochrane Database Syst Rev 2020;11:CD003633.
5. Kreisler A, Djelad S, Simonin C, et al. Does ultrasound-guidance improve the outcome of botulinum toxin injections in cervical dystonia? Rev Neurol (Paris) 2022;178:591-602.

DOI: 10.1056/NEJMc2314018

Convalescent Plasma for Covid-19–Induced ARDS

TO THE EDITOR: Misset et al. (Oct. 26 issue)[1] reported a significant reduction in mortality among patients with acute respiratory distress syndrome (ARDS) associated with Covid-19 who received plasma from convalescent patients previously hospitalized for Covid-19–associated ARDS. The sex

and age of the plasma donors are not reported. Moreover, neither the donors nor the recipients were tested for the presence of autoantibodies that neutralize type I interferons. Such testing would have been important, given that preexisting circulating autoantibodies that neutralize type I interferons may underlie approximately 15% of cases of life-threatening Covid-19 pneumonia and approximately 20% of Covid-19–related deaths.[2,3] Moreover, in both the general population and the population of patients with Covid-19, the prevalence of these autoantibodies is higher among men than women and is higher among persons older than 65 years of age than younger persons.[3,4] The beneficial, neutral, or detrimental effect of convalescent plasma should be analyzed by taking into account demographic data and test results for autoantibodies that neutralize type I interferons from both donors and recipients.

Alessandro Borghesi, M.D., Ph.D.

San Matteo Research Hospital
Pavia, Italy
a.borghesi@smatteo.pv.it

Jean-Laurent Casanova, M.D., Ph.D.

Rockefeller University
New York, NY

No potential conflict of interest relevant to this letter was reported.

1. Misset B, Piagnerelli M, Hoste E, et al. Convalescent plasma for Covid-19–induced ARDS in mechanically ventilated patients. N Engl J Med 2023;389:1590-600.
2. Bastard P, Rosen LB, Zhang Q, et al. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. Science 2020;370:eabd4585.
3. Bastard P, Gervais A, Le Voyer T, et al. Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. Sci Immunol 2021;6:eabl4340.
4. Manry J, Bastard P, Gervais A, et al. The risk of COVID-19 death is much greater and age dependent with type I IFN autoantibodies. Proc Natl Acad Sci U S A 2022;119(21):e2200413119.

DOI: 10.1056/NEJMc2313675

TO THE EDITOR: Misset et al. provided evidence that convalescent plasma containing high levels of neutralizing antibodies (85th percentile or greater) administered within 5 days after the initiation of mechanical ventilation reduced the 28-day mortality among patients with Covid-19–induced ARDS. Why did this trial show a mortality benefit of convalescent plasma, although previous studies involving similar patients did not? The answer probably arises from the authors' attentiveness to the timing of the administration of convalescent plasma, as well as the use of convalescent plasma with high neutralizing antibody titers. A benefit from the early administration of convalescent plasma is consistent with the biologic principles of antibody therapy[1] and the totality of clinical evidence in the broader population of patients with Covid-19.[2] The results of this trial suggest the possibility that some patients with Covid-19 have respiratory failure that is reversible with antiviral antibodies. A mortality benefit has previously been observed in patients with Covid-19 and hematologic cancer who were admitted to the intensive care unit and were treated with convalescent plasma, a finding that may be related to the propensity for prolonged viremia in this population.[3] Thus, future interventional studies for respiratory viruses should be attentive to patient populations that might benefit from later treatment.

Jonathon W. Senefeld, Ph.D.

University of Illinois Urbana-Champaign
Urbana, IL
senefeld@illinois.edu

Jeffrey P. Henderson, M.D., Ph.D.

Washington University in St. Louis
St. Louis, MO

Michael J. Joyner, M.D.

Mayo Clinic
Rochester, MN

No potential conflict of interest relevant to this letter was reported.

1. Casadevall A, Joyner MJ, Pirofski L-A, et al. Convalescent plasma therapy in COVID-19: unravelling the data using the principles of antibody therapy. Expert Rev Respir Med 2023;17:381-95.
2. Senefeld JW, Gorman EK, Johnson PW, et al. Rates among hospitalized patients with COVID-19 treated with convalescent plasma: a systematic review and meta-analysis. Mayo Clin Proc Innov Qual Outcomes 2023;7:499-513.
3. Thompson MA, Henderson JP, Shah PK, et al. Association of convalescent plasma therapy with survival in patients with hematologic cancers and COVID-19. JAMA Oncol 2021;7:1167-75.

DOI: 10.1056/NEJMc2313675

TO THE EDITOR: Misset et al. reported that treatment with Covid-19 convalescent plasma led to reduced mortality in patients receiving mechanical ventilation. This finding is unexpected because antibody-based therapies work best early in the disease course.[1] Since the trial participants had advanced disease, it might be predicted that convalescent plasma would have no benefit because inflammation, rather than viral replication, is considered to be the main driver of progressive Covid-19. However, convalescent plasma contains

both neutralizing antibodies that mediate viral elimination and nonneutralizing antibodies that can modulate inflammation.[2] Patients receiving treatment with convalescent plasma have been shown to have lower levels of serum inflammatory mediators than those not receiving treatment.[3] The ability of convalescent plasma to mediate antiviral activity and modulate inflammation is consistent with the damage–response framework of microbial pathogenesis,[4] which suggests that damage may be reduced by eliminating the virus or dampening inflammation. Among participants in the trial by Misset et al. who received convalescent plasma, the treatment may have cleared viral debris and residual virus while mediating antiinflammatory activity that prevented further inflammation and promoted resolution of lung damage, thus having effects consistent with greater survival 2 weeks after treatment. The benefit of convalescent plasma observed in this trial calls for a better understanding of the mechanisms of efficacy.

Arturo Casadevall, M.D., Ph.D.

Johns Hopkins School of Public Health
Baltimore, MD
acasadel@jhu.edu

Shmuel Shoham, M.D.

Johns Hopkins School of Medicine
Baltimore, MD

Liise-anne Pirofski, M.D.

Albert Einstein College of Medicine
New York, NY

No potential conflict of interest relevant to this letter was reported.

1. Casadevall A, Pirofski L-A, Joyner MJ. The principles of antibody therapy for infectious diseases with relevance for COVID-19. mBio 2021;12(2):e03372-20.
2. Natarajan H, Crowley AR, Butler SE, et al. Markers of polyfunctional SARS-CoV-2 antibodies in convalescent plasma. mBio 2021;12(2):e00765-21.
3. Bandopadhyay P, D'Rozario R, Lahiri A, et al. Nature and dimensions of systemic hyperinflammation and its attenuation by convalescent plasma in severe COVID-19. J Infect Dis 2021;224:565-74.
4. Casadevall A, Pirofski L-A. The damage-response framework of microbial pathogenesis. Nat Rev Microbiol 2003;1:17-24.

DOI: 10.1056/NEJMc2313675

THE AUTHORS REPLY: Borghesi and Casanova suggest that the prevalence of autoantibodies that neutralize type I interferons would influence the effect of Covid-19 convalescent plasma. In our trial, since convalescent plasma was selected according to its ability to neutralize viral cultures, the donors were not a random sample. The donors had a median age of 49 years (interquartile range, 36 to 53). Convalescent plasma containing these autoantibodies would have neutralized endogenous interferon in the recipients, and the observed benefit would be greater with the use of convalescent plasma that did not contain autoantibodies. There were no selection criteria for the recipients other than the presence of Covid-19–induced ARDS and the use of invasive mechanical ventilation. They were not tested for antibodies. If 15 to 20% of the trial patients had these autoantibodies, the trial population would have been representative of the population of patients with critical Covid-19. If this percentage exceeded 20%, the effect of convalescent plasma may have been underestimated. If this percentage was less than 15%, the effect may have been overestimated.

We agree with Senefeld et al. that an evaluation of Covid-19 convalescent plasma therapy should be conducted in patients with various causes of immunosuppression because the proportion of these patients admitted for critical Covid-19 has increased since 2022.[1] Casadevall et al. question the mechanisms of action of Covid-19 convalescent plasma. Increased viral clearance is probably an important factor,[2] but this area should be investigated further.

Benoît Misset, M.D.
Daniel Desmecht, D.V.M., Ph.D.

Liège University
Liège, Belgium
benoit.misset@chuliege.be

Pierre-François Laterre, M.D.

Mons University
Mons, Belgium

Since publication of the article, the authors report no further potential conflict of interest.

1. Intensive Care National Audit and Research Centre. Reports: COVID-19 report. June 2023 (https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports).
2. Carroll TD, Wong T, Morris MK, et al. Administration of vaccine-boosted COVID-19 convalescent plasma to SARS-CoV-2 infected hamsters decreases virus replication in lungs and hastens resolution of the infection despite transiently enhancing disease and lung pathology. August 23, 2023 (https://www.biorxiv.org/content/10.1101/2023.08.22.553458v1). preprint.

DOI: 10.1056/NEJMc2313675