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Opinion of the AvATher Working Group on the Use of COVID-19 Convalescent Plasma (CCP)

Response to the request from the Directorate General for Health (DGS) regarding the evaluation of the role of COVID-19 convalescent plasma (CCP) in the management of immunocompromised patients hospitalized for COVID-19–related complications

04 December 2025

Request:
The French Ministry of Health (DGS) has asked the ANRS MIE AvATher working group to assess the current role of COVID-19 convalescent plasma (CCP) in the management of immunocompromised patients hospitalized with COVID-19-related complications, and to provide an opinion on whether to maintain or suspend the Therapeutic Use Protocol (PUT).

This request follows an alert issued by the EFS regarding a probable CCP shortage by early 2026 due to increasing difficulties in recruiting eligible donors, along with a significantly reduced national stock (150 units as of 22 September 2025, sufficient for only 37 patients). It also reflects the marked and ongoing decline in CCP use under the PUT since 2023 (1,739 patients in 2022, 841 in 2023, 322 in 2024, and approximately seven per month in 2025), as well as the absence of any inclusions to date in the CCP arm of the REMAP-CAP trial in France despite authorization for 20 participants.

A. Reminder of the AvATher Working Group's Previous Opinion on COVID-19 Convalescent Plasma (2023)[1]

In 2023, the AvATher Working Group evaluated the role of COVID-19 convalescent plasma (CCP) in the management of COVID-19 among immunocompromised patients. In this opinion, the group noted that although the available evidence did not support recommending CCP for the early treatment of COVID-19, several studies suggested a potential benefit in immunocompromised individuals with prolonged SARS-CoV-2 replication. Nevertheless, the group concluded that the overall level of evidence remained insufficient to justify routine clinical use. AvATher emphasized, however, that given the therapeutic impasse faced by certain patients, the positive signals reported in the literature, the absence of major safety concerns to date, and the pending results of clinical trials, CCP should continue to be evaluated within a

[1] https://anrs.fr/wp-content/uploads/2024/04/avis-avater-du-01-aout-2023-pcc.pdf

standardized clinical research framework, including the analysis of data already collected under the Temporary Therapeutic Use Protocol (PUT).

B. Position of international agencies regarding the use of COVID-19 convalescent plasma

1. United States - regulatory agencies and clinical recommendations

- **FDA/CDC**

According to the most recent FDA recommendations (July 2024)[2], COVID-19 convalescent plasma (CCP) remains authorized under the Emergency Use Authorization (EUA) exclusively for the treatment of COVID-19 in patients with a disease that causes immunosuppression or who are receiving immunosuppressive treatments, whether they are being treated on an outpatient or inpatient basis. This position reflects the FDA's conclusion that high-antibody-titer CCP could be effective in this population, particularly given their low vaccine response, risk of prolonged infection, and decreased effectiveness of monoclonal antibodies against emerging variants. The FDA has reviewed new studies published since the EUA review in 2021 and continues to consider CCP a treatment option for immunocompromised patients. The CDC does not make independent recommendations and refers to the FDA's regulatory framework and the IDSA's clinical recommendations[3].

- **IDSA**

The recommendations of the Infectious Diseases Society of America (IDSA), updated in February 2023 and still in effect[4], take a more cautious stance on the use of COVID-19 convalescent plasma. In immunocompetent hospitalized patients, the IDSA recommends against the use of convalescent plasma (strong recommendation, moderate level of evidence). In immunocompromised hospitalized patients, the IDSA also suggests not using it routinely (conditional recommendation, very low level of evidence), due to persistent uncertainty about the clinical benefit, particularly in terms of mortality. However, in outpatients at high risk of progression to severe disease and with no other treatment options, the IDSA suggests the use of convalescent plasma with high antibody levels, administered early after the onset of symptoms (conditional recommendation, low level of evidence).

These positions illustrate the contrast between regulatory approval based on therapeutic deadlock situations (FDA) and clinical recommendations based on a strict assessment of the level of evidence, which remains limited (IDSA).

2. NIH

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-investigational-and-licensed-covid-19-convalescent-plasma.
[3] https://www.cdc.gov/covid/hcp/clinical-care/outpatient-treatment.html
[4] https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

The NIH (National Institutes of Health) supported several randomized clinical trials, including the **PassITON**[5] and **CONTAIN**[6] trials conducted in hospitalized adults, which showed no clinical benefit, as well as the outpatient **C3PO** trial, which also concluded that early administration of high-dose CCP did not prevent disease progression in high-risk patients and was stopped due to lack of efficacy. Although CCP was well tolerated, none of these rigorous trials demonstrated efficacy in immunocompetent patients. In immunocompromised individuals, NIH recommendations indicate that there is insufficient data to recommend or reject the use of CCP in immunocompromised patients, leaving room for clinical judgment on a case-by-case basis.

3. European Myeloma Network[7]

A recent consensus from the European Myeloma Network indicates that convalescent plasma has limited value in the post-pandemic era. This conclusion reflects the availability of effective early antiviral treatments and the generally milder presentation of the disease with the variants currently in circulation. Although patients with multiple myeloma remain at high risk for severe forms of COVID-19 and often have reduced humoral responses after vaccination, the network emphasizes that antivirals such as nirmatrelvir/ritonavir, molnupiravir (not available in France), and remdesivir should be prioritized, while convalescent plasma no longer plays a significant role in routine management.

C. Scientific data on COVID-19 convalescent plasma (since the last AvATher opinion dated August 1, 2023)

Bloch et al. (2023)[8] report that COVID-19 convalescent plasma (CCP) is considered a safe and potentially effective treatment in immunocompromised patients with COVID-19, whether in the context of acute infection or prolonged or persistent viral replication. According to this expert consensus, high-titer CCP retains broad neutralizing activity against circulating variants (2023), including those against which monoclonal antibodies have lost their effectiveness, due to its polyclonal composition. However, it can be argued that this neutralizing activity measured in vitro results from the combined action of IgG, IgA, and IgM, the latter of which may have high avidity, including for variants, and strong neutralizing capacity, but also have a short half-life and therefore a low protective effect in vivo. The activity of the IgG component of these CCPs

[5] https://ncats.nih.gov/news-events/news/nih-expands-clinical-trials-to-test-convalescent-plasma-against-covid-19.
[6] https://ncats.nih.gov/news-events/news/2022/statement-on-nih-study-testing-convalescent-plasma-in-hospitalized-patients.
[7] https://www.myeloma-europe.org/publications/management-of-patients-with-multiple-myeloma-and-covid-19-in-the-post-pandemic-era-a-consensus-paper-from-the-european-myeloma-network-emn/?highlight=convalescent+plasma.
[8] Bloch EM, Focosi D, Shoham S, Senefeld J, Tobian AAR, Baden LR, Tiberghien P, Sullivan DJ, Cohn C, Dioverti V, Henderson JP, So-Osman C, Juskewitch JE, Razonable RR, Franchini M, Goel R, Grossman BJ, Casadevall A, Joyner MJ, Avery RK, Pirofski LA, Gebo KA. Guidance on the Use of Convalescent Plasma to Treat Immunocompromised Patients With Coronavirus Disease 2019. Clin Infect Dis. 2023 Jun 8;76(11):2018-2024. doi: 10.1093/cid/ciad066.

should be compared with that of monoclonal antibodies, which are IgG, the only subclass that persists for a long time in vivo.

The systematic review and meta-analysis published in JAMA Network Open by **Senefeld et al (2023)**[9] included eight controlled studies (three randomized clinical trials and five cohort studies with matched, treated-control groups), involving 1,774 immunocompromised patients (469 treated with CCC and 1,305 controls) treated before the omicron era (mainly delta). CPP transfusion was associated with a reduction in all-cause mortality compared to standard treatment, with a combined relative risk of 0.63 (95% CI: 0.50-0.79). In randomized trials alone, the relative risk was 0.58 (95% CI: 0.34-0.98), and no serious adverse events related to CCP were reported. The certainty of the evidence was rated as low to moderate due to the risk of bias, heterogeneity of the studies, and reliance on observational data, especially since many patients were treated late (median delay of 17 days after symptom onset). Overall, the authors conclude that CPP may provide a mortality benefit in hospitalized immunocompromised patients, while emphasizing the need for further controlled trials.

The Norwegian **NORPLASMA** observational study[10] evaluated 79 patients with COVID-19 treated with convalescent plasma, including 59 immunocompromised individuals. The treatment was well tolerated, with no serious adverse events reported. Overall mortality was high (39%), but lower among immunocompromised patients (34%) than among immunocompetent patients (55%). The authors conclude that convalescent plasma is safe and may provide clinical benefit in immunocompromised patients, while acknowledging the limitations inherent to uncontrolled observational data.

D. Updated recommendations from the AvATher group concerning the role of CCP in the therapeutic management of immunocompromised patients

In light of the available data, the AvATher group notes that the level of evidence supporting the efficacy of convalescent plasma (CP) in the management of immunocompromised patients with COVID-19 has not progressed significantly since the previous opinion published in 2023. The literature does not provide robust evidence of clinical benefit in controlled studies.

In addition, due to ongoing operational difficulties, maintaining sufficient stocks of plasma with high antibody levels has become increasingly difficult, due to constraints in donor recruitment and a decrease in suitable serological profiles (notably due to a decrease in vaccination and less use of virological diagnosis in cases of suggestive symptoms).

[9] Senefeld JW, Franchini M, Mengoli C, Cruciani M, Zani M, Gorman EK, Focosi D, Casadevall A, Joyner MJ. COVID-19 Convalescent Plasma for the Treatment of Immunocompromised Patients: A Systematic Review and Meta-analysis. JAMA Netw Open. 2023 Jan 3;6(1):e2250647. doi: 10.1001/jamanetworkopen.2022.50647.

[10] Nissen-Meyer LSH, Macpherson ME, Skeie LG, Hvalryg M, Llohn AH, Steinsvåg TT, Fenstad MH, Tveita A, Kristoffersen EK, Sundic T, Lund-Johansen F, Vaage JT, Flesland Ø, Dyrhol-Riise AM, Holter JC, Hervig TA, Fevang B. COVID-19 patients treated with convalescent plasma. Tidsskr Nor Laegeforen. 2023 Jul 26;143(11). English, Norwegian. doi: 10.4045/tidsskr.22.0577.

The potential population of recipients likely to benefit from CCP would therefore only include a very small subgroup of immunocompromised patients:

- those with no alternative treatment options, particularly those without neutralizing antibodies and at very high risk of mortality upon admission to intensive care.
- and/or with persistent SARS-CoV-2 replication preventing access to essential subsequent treatments for severe comorbidity, such as CAR-T cells.

These exceptional situations may justify individualized discussion, but cannot justify widespread use.

CCPs should only be used in regulated and protocolized clinical settings, even though the lack of inclusions in the REMAP-CAP trial in France highlights the current difficulties and limitations of this approach.

The issue of maintaining CCP production and supply chains also arises in the context of a broader strategy for preparing for health crises, which should ultimately include preparations of specific purified immunoglobulins (IgG). However, little progress has been made on these structural and strategic aspects.

The group therefore regrets the lack of progress following the recommendations issued in 2023:
(i) Maintaining a functional supply chain for high-titer CCPs;
(ii) Developing rapid response immunoglobulin production capacities;
(iii) Integrating antibody-based therapies into national preparedness plans.

Finally, the group noted that some international agencies, particularly in the United States, continue to maintain monoclonal antibodies in their therapeutic frameworks as a precautionary measure, in case future variants become sensitive again. This approach reflects the uncertainty surrounding the evolving virological landscape and similarly calls for caution before considering a complete withdrawal of CCP.

Conclusion

In light of all the available data and the group's deliberations, AvATher considers that, at this stage, CCP has not been sufficiently proven to play a role in the therapeutic management of COVID-19 in immunocompromised patients. The level of evidence remains insufficient, the expected benefit modest at best, and the scientific data unchanged since 2023. The group cannot therefore recommend CCP in routine clinical practice or as a proven therapeutic option.

However, exceptional use on a case-by-case basis may be considered for a very small subgroup of highly selected immunocompromised patients, particularly those with persistent viral replication preventing access to further treatments essential for severe comorbidity, and those with no therapeutic alternatives, particularly those without

neutralizing antibodies and at very high risk of mortality upon admission to intensive care. It will then be up to the competent authorities to decide whether they wish to maintain this option in these specific situations. Any case-by-case use must remain strictly limited to structured and protocolized clinical settings (e.g., PUT or clinical trial). The group emphasizes that discontinuation of PUT should not be considered without a comprehensive assessment of the consequences for particularly vulnerable patients who are likely to benefit from it.

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