Commentary

Inclusion of cryoprecipitate, pathogen-reduced, in the WHO model lists of essential medicines for adults and children: a call for action

*On behalf of the Working Party for "Global Blood Safety" of the International Society of Blood Transfusion

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Arrived: 28 October 2023
Revision accepted: 16 January 2024
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The treatment of people with congenital or acquired bleeding disorders is a pressing global health concern. According to the World Federation of Hemophilia (WFH), 70-80% of hemophilia patients, mostly in low –and lower middle– income countries (LIC/LMICs) as defined by the World Bank[1], lack adequate treatment[2,3]. Protein replacement with industrially fractionated plasma-derived coagulation factor concentrates (CFCs) and alternative recombinant products are the drugs of choice for preventing and treating bleeding in inherited bleeding disorders (IBDs) including hemophilia A, hemophilia B, and von Willebrand Disease. Fibrinogen concentrates are vital to provide replacement therapy in acute massive hemorrhage, such as those experienced by women during childbirth, highlighting their critical role in preserving lives and reducing morbidity worldwide. However, access to these products is insufficient in LIC/LMICs due to limited resources[3] and even low-dose prophylaxis remains out of reach for most patients with IBDs in these countries. The costs of CFCs can be prohibitive, reaching up to 10,000 USD per day of treatment in life-threatening situations in some high-income countries (HIC). Routine prophylaxis costs over several hundred thousand USD per patient per year, and even higher for patients with anti-factor VIII inhibitors[3-5]. However, the availability of several generations of CFCs, including standard and extended half-life recombinant CFCs and their bifunctional monoclonal antibody mimetics, has reduced costs in some HICs, and some LMICs have successfully managed to obtain competitive costs for CFCs, through effective and efficient procurement programs[6].

The very recent inclusion of cryoprecipitate, pathogen-reduced (Cryo-PR), in the World Health Organization (WHO) Model List of Essential Medicines for adults (EML) and for children (EMLc) sends a strong signal[7]. This inclusion underscores the importance of allocating sufficient resources for local production and governmental regulation of Cryo-PR as a reasonably safe and potentially more affordable treatment in LIC/LMICs for acute bleeding, including post-partum hemorrhage, and possibly low-dose prophylaxis in various IBDs[8] when access to CFCs is lacking. Cryo-PR is by far a safer alternative to non-pathogen-reduced (native) cryoprecipitate, particularly in regions with a high prevalence of infections such as HIV, hepatitis B, and hepatitis C. The use of native cryoprecipitate in these areas carries unacceptable risks due to the prevalence of these infections in blood donors[9], suboptimal donation testing[10], and the additive infectious risks from repeated exposures to products prepared even from small plasma pools[11,12]. Consequently, in these settings Cryo-PR rather than native cryoprecipitate should be the strictly preferred option. In countries with a very high prevalence of HIV, hepatitis

B, or hepatitis C viruses (as well as non-enveloped viruses) additional implementation of NAT testing of the contributing blood donations can further enhance the margin of virus safety by rejecting detectably contaminated units.

The application to WHO for inclusion of Cryo-PR in the EMLs was submitted jointly by the International Society of Blood Transfusion (ISBT) and the WHO Blood and Other Products of Human Origin Team[13]. Additionally, WFH and several other prominent stakeholder organizations submitted letters to WHO supporting the application. Understandably, cost considerations were discussed extensively in the application. It was highlighted that Cryo-PR can be cost-competitive with commercial concentrates of fibrinogen[14,15], as well as plasma derived and recombinant CFC, when available, as seen in Egypt and Thailand[13,16]. Pathogen reduction of small pools of cryoprecipitate rather than individual units further enhances cost-efficiency of preparing Cryo-PR[13]. Still, even in LIC/LMICs where the cost of locally produced Cryo-PR may be favorable relative to the procurement cost of CFCs, this should not override the importance of providing patients with CFCs or alternative recombinant products when these medically preferred therapies are available and affordable. Governments should indeed strive to support patient access to preferred products through efficient procurement systems even at potentially higher costs. Nevertheless, as an interim measure, we call upon governments to prioritize the availability of Cryo-PR, rather than native cryoprecipitate, in countries where advanced therapies for bleeding disorders are not yet accessible. Local preparation of quality-assured Cryo-PR represents a pragmatic step toward improving the standard of care for bleeding patients in LICs/LMICs where access to preferred products is constrained. At the same time, local preparation of quality-assured Cryo-PR serves as a stepwise advancement towards a national program of quality management of the blood system. Furthermore, assuring the quality of plasma can potentially enable a national program for fractionation of domestic plasma as a means to obtain CFCs and other essential industrially-manufactured plasma protein products[17].

As reported in an executive summary of the relevant WHO Expert Committee[18], the Committee "recommended the inclusion of pathogen-reduced cryoprecipitate in the core list of the EML and EMLc with a square box to indicate non-pathogen-reduced cryoprecipitate as a therapeutic alternative". This core listing highlights Cryo-PR as the preferred option but, in the current edition, also recognizes a role of native cryoprecipitate as a secondary alternative. This is especially relevant in low-income countries where no other options may be available. We acknowledge the existing controversy, regarding the use of native cryoprecipitate[19]. Still, it is noteworthy that the Council of Europe (CoE) Guide recognizes native cryoprecipitate alongside Cryo-PR[20]. Furthermore, in the United States, native cryoprecipitate is still authorized under the name Cryoprecipitated AHF, although it is considered a second-line therapy. This aligns with its listing in the Essential Medicines List (EML/EMLc). While it is important to acknowledge that the CoE Guide and the U.S. FDA recognize native cryoprecipitate, it is crucial to emphasize that these authorities operate in high-income countries with stringent virus safety measures that may not be present in LMICs. Conversely, the use of native cryoprecipitate in LMICs carries significant risks due to the lack of these comprehensive safety measures and high prevalence of transfusion transmissible infections in blood donors. As such, the recommendation for Cryo-PR in LMICs is based on its improved virus safety profile in contexts where these optimal safety protocols are not yet in place. Considering that the WHO listed Cryo-PR and not native cryoprecipitate as an essential medicine, the inclusion in the WHO EMLs of native cryoprecipitate as an alternative product should drive national efforts to ensure its quality and safety, pending access to Cryo-PR. These would include better funding and oversight for blood establishments, selection of safer donors, assuring use of highly effective infectious disease testing and optimization of component processing. At the same time, any national commitment to preparation of native cryoprecipitate should lay the groundwork for further safety enhancements including pathogen reduction. Importantly, pathogen reduction when introduced should not be taken as a substitute for implementation of good manufacturing practices in blood collection, testing and processing[21].

In summary, access to CFCs in LIC/LMICs regrettably is limited, resulting in otherwise preventable morbidity and mortality. Cryoprecipitate when properly

pathogen-reduced offers a much safer alternative for treating acute bleeding associated with various coagulopathies, including post-partum hemorrhage, when preferred therapies are not available. Its inclusion in the WHO EML and EMLc now recognizes its essential role in a national health system to meet the priority healthcare needs of the population. This core listing should encourage governments to include Cryo-PR in their national EMLs, thereby prioritizing allocation of resources for its local preparation and regulatory oversight while raising the awareness of healthcare providers. Local preparation of quality assured Cryo-PR represents a pragmatic step towards improving the standard of care for bleeding patients in LICs/LMICs where access to preferred products is constrained. Concurrently, preparation of quality-assured Cryo-PR advances the blood system as a whole. Addressing the needs of individuals with congenital or acquired bleeding disorders is an integral part of a wider global health improvement, aiming to ensure safe, accessible and equitable treatment for all, and to act against global inequality of care.

ACKNOWLEDGMENTS

JE, JCF, MS, and TB are members of the sub-group for "Safe Plasma Proteins" of the Working Party for "Global Blood Safety" of the International Society of Blood Transfusion.

AUTHORS' CONTRIBUTION

JE and TB conceptualized the writing and drafted the manuscript. All Authors provided comments and contributed to writing of the final manuscript and approved the final version for publication.

The Authors declare no conflicts of interest.

REFERENCES

1. New World Bank country classifications by income level: 2022-2023 Available at: https://blogs.worldbank.org/opendata/new-world-bank-country-classifications-income-level-2022-2023. Accessed on 25/10/2023.
2. Pierce GF, Adediran M, Diop S, Dunn AL, Ekiaby ME, Kaczmarek R, et al. Achieving access to haemophilia care in low-income and lower-middle-income countries: expanded Humanitarian Aid Program of the World Federation of Hemophilia after 5 years. Lancet Haematol 2022; 9: e689-e697. doi: 10.1016/S2352-3026(22)00209-5.
3. Srivastava A. The case for equitable haemophilia care. Lancet Haematol 2021; 8: e626. doi:10.1016/S2352-3026(21)00132-0.
4. Batt K, Schultz BG, Caicedo J, Hollenbeak CS, Agrawal N, Chatterjee S, et al. A real-world study comparing pre-post billed annualized bleed rates and total cost of care among non-inhibitor patients with hemophilia A switching from FVIII prophylaxis to emicizumab. Curr Med Res Opin 2022; 38: 1685-1693. doi: 10.1080/03007995.2022.2105072.
5. Srivastava A, Santagostino E, Dougall A, Kitchen S, Sutherland M, Pipe SW, et al. WFH guidelines for the management of hemophilia, 3rd edition. Haemophilia 2020; 26 Suppl 6: 1-158. doi:10.1111/hae.14046.
6. O'Mahony B. Guide to national tenders for the purchase of clotting factor concentrates - 2nd edition. Available from: https://www1.wfh.org/publication/files/pdf-1294.pdf. Accessed on 25/06/2023.
7. World Health Organization. The selection and use of essential medicines 2023: web annex A: World Health Organization model list of essential medicines: 23rd list (2023). Available at: https://apps.who.int/iris/handle/10665/371090. Accessed on 28/08/2023.
8. El Ekiaby M, Burnouf T, Goubran H, et al. Role of the mini-pool cryoprecipitate technology for cost-saving and guarantee of local Factor VIII, Von Willebrand Factor and Fibrinogen product supply: Egypt experience. Ann Blood 2018; 3: 22. doi: 10.21037/aob.2018.02.07.
9. World Health Organisation. Global status report on blood safety and availability 2021 Available at: https://www.who.int/publications/i/item/9789240051683. Accessed on 25/10/2023.
10. Jacobs JW, Stephens LD, Milner DA Jr, Bloch EM, Goel R, Tobian AAR, et al. Survey of blood collection and transfusion practices among institutions in Africa. Transfusion 2023; 63: 1849-1858. doi:10.1111/trf.17501.
11. Lynch TJ, Weinstein MJ, Tankersley DL, Fratantoni JC, Finlayson JS. Considerations of pool size in the manufacture of plasma derivatives. Transfusion 1996; 36: 770-775. doi: 10.1046/j.1537-2995.1996.36996420751.x.
12. Evatt B, Austin H, Leon G, Ruiz-Sáez A, de Bosch N. Hemophilia treatment. Predicting the long-term risk of HIV exposure by cryoprecipitate. Haemophilia 2000; 6 (Suppl 1): 128-132. doi: 10.1046/j.1365-2516.2000.00057.x.
13. Application submitted by the International Society of Blood Transfusion (ISBT) for inclusion on the WHO EML and EMLc. Available at: https://cdn.who.int/media/docs/default-source/essential-medicines/2023-eml-expert-committee/applications-for-addition-of-new-medicines/a11_cryoprecipitate-pr.pdf?sfvrsn=87f1db91_3. Accessed on 20/10/2023.
14. Okerberg CK, Williams LA 3rd, Kilgore ML, Kim CH, Marques MB, Schwartz J, et al. Cryoprecipitate AHF vs. fibrinogen concentrates for fibrinogen replacement in acquired bleeding patients - an economic evaluation. Vox Sang 2016; 111: 292-298. doi: 10.1111/vox.12417.
15. Novak A, Stanworth SJ, Curry N. Do we still need cryoprecipitate? Cryoprecipitate and fibrinogen concentrate as treatments for major hemorrhage - how do they compare? Expert Rev Hematol 2018; 11: 351-360. doi:10.1080/17474086.2018.1458610.
16. Burnouf T, Epstein J, Faber JC, Smid WM; Working party for global blood safety of the international society of Blood Transfusion. Stepwise options for preparing therapeutic plasma proteins from domestic plasma in low- and middle-income countries. Vox Sang 2024; 119: 102-109. doi: 10.1111/vox.13516.
17. World Health Organization. Guidance on increasing supplies of plasma-derived medicinal products in low- and middle-income countries through fractionation of domestic plasma. Available at: https://apps.who.int/iris/handle/10665/340171. Accessed on 20/10/2023.
18. World Health Organization. The selection and use of essential medicines 2023. Executive Summary of the report of the 24th WHO Expert Committee on Selection and Use of Essential Medicines. Available at: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2023.01. Accessed on 28/08/2023.
19. Farrugia A. The World Health Organisation's list of essential medicines and haemophilia treatment products. Haemophilia, 2023; 29: 1387-1389. doi: 10.1111/hae.14879.
20. European Directorate for the Quality of Medicine and Health care. 21st edition of the Guide to the preparation, use and quality assurance of blood components (Blood Guide). Available at: https://www.edqm.eu/en/-/edqm-publishes-21st-edition-of-the-blood-guide-providing-state-of-the-art-guidance-for-healthcare-professionals. Accessed on 28/08/2023.
21. World Health Organization. WHO guidelines on good manufacturing practices for blood establishments, Annex 4, TRS No 961. Available at: https://www.who.int/publications/m/item/gmp-for-blood-establishments -annex-4-trs-no-961. Accessed on 01/09/2023.