WHO Blood Regulators Network (BRN)
Position Statement on Use of Pathogen-Reduced Cryoprecipitate in Settings Where Commercial Clotting Factor Concentrates are Unavailable or Unaffordable*

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Background

An enormous therapeutic gap exists between low- and medium-income countries compared with high-income countries regarding use of cryoprecipitate versus the availability and usage of “modern” virally safe commercial clotting factor concentrates (CFC) or other therapeutic options to treat bleeding disorders including hemophilia A and von Willebrand disease. According to the World Federation of Hemophilia, 75 to 80% of all patients with hemophilia lack access to any form of treatment (1), and this figure has not changed in the last 20-30 years (2). As an interim strategy, lack of access to safe and affordable commercial CFC to treat hemophilia A, and von Willebrand Disease in resource limited settings can be addressed through strengthening of national blood systems to enable local production of quality pathogen-reduced cryoprecipitate.

The development of cryoprecipitate in the 1960’s was a major advancement in the treatment of hemophilia A and von Willebrand Disease, replacing plasma transfusion by a more effective and better tolerated product. Cryoprecipitate, which contains high concentrations of Factor VIII (FVIII) and von Willebrand Factor (VWF) compared with plasma, also contains high levels of fibrinogen (as well as Factor XIII and fibronectin.) This makes cryoprecipitate an alternative therapeutic option compared with CFC for fibrinogen replacement in inherited and acquired disorders of fibrinogen, e.g. when given to treat hypofibrinogenemia in massive hemorrhage including obstetrical bleeding (3). Cryoprecipitate is still used throughout the world. However, as a non-pathogen-reduced and pooled plasma product, it carries risk for transmission of pathogens like parasites, bacteria and viruses, including human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) even when blood donations are properly screened. Transmission of blood borne pathogens from cryoprecipitate is rare in high-income countries where robust donor screening practices and testing exist. However, the risk is substantially higher in low- and medium-income countries where blood donor screening practices, viral prevalence rates and testing methods differ. In high-income countries, since the 1970’s, use of cryoprecipitate to prevent and treat bleeding in hemophilia A and von Willebrand Disease has been superseded by the availability of commercially prepared plasma-derived and recombinant DNA-derived concentrates of Factor VIII and von Willebrand Factor, which are virtually virus-safe and available in lyophilized form (4). Unfortunately, in many low- and medium-income countries, access to these preferred therapies is still limited or lacking, resulting in otherwise preventable mortality and severe morbidity in patients suffering from these diseases (5).
Largely because of costs, it is unlikely in resource constrained settings that availability of commercial CFC will improve significantly in the foreseeable future. For this reason, consideration needs to be given to the use of pathogen-reduced cryoprecipitate.

Limitations and Uncertainties

Strengthening national capacities for the local preparation of pathogen-reduced cryoprecipitate to meet patient needs in hemophilia A, von Willebrand Disease and fibrinogen disorders is intended to improve the availability and accessibility of a therapeutic resource in limited settings. However, the feasibility, cost-effectiveness and clinical utility of this approach need to be considered in the national context. The challenge to establish local production under GMP-like conditions, including regulatory oversight, are not trivial, but if implemented will also have a beneficial impact on quality and safety of labile blood components. The issues of cold-chain in preparation, storage and transport of the product (especially freezing), and the complexity of potential home-treatment relying on a frozen product with a brief shelf-life post-thaw need to be addressed from a logistical and educational perspective to prevent bacterial contamination and to avoid alterations of the product due to temperature excursions. Dosing for episodic treatment, prophylaxis and management of anti-FVIII inhibitors also need to be addressed by clinicians with attention to possible under-treatment in severe bleeding and surgery, risks of fluid and/or protein overload, and potential for transfusion-related lung injury (TRALI). Furthermore, although not as harmful as the lipid enveloped viruses HIV, HBV and HCV that are highly sensitive to inactivation methods, the unmitigated risks for transmission of non-enveloped viruses resisting pathogen reduction (i.e. hepatitis A virus, hepatitis E virus and human parvovirus B19) may require additional precautionary measures when feasible.

BRN Position

Plasma-derived and recombinant CFC are recognized by relevant professional organizations as the treatment of choice for hemophilia A and von Willebrand Disease based on their established quality, safety, efficacy and ease of use. However, resource limitations in many low- and medium-income countries currently make these products unavailable for the vast majority of patients, resulting in significant morbidity and mortality from otherwise preventable bleeding. In these settings, consideration should be given to local production of pathogen-reduced cryoprecipitate made under Good Preparation Practices (6) in blood establishments from pooled whole blood-derived plasma or pooled cryoprecipitates using technologies that have been approved by advanced regulatory authorities. Plasma units obtained as a byproduct of whole blood collection can provide a stable and ongoing local source for preparation of pathogen-reduced cryoprecipitate in an organized and regulated national blood system. Pathogen-reduced cryoprecipitate also can provide a safe source of fibrinogen when used for treatment of fibrinogen disorders in various medical conditions including acquired deficiencies due to massive hemorrhage in trauma or obstetrics.
Where feasible, non-pathogen-reduced cryoprecipitate should be replaced by pathogen-reduced cryoprecipitate in the treatment of patients with hemophilia A, von Willebrand Disease and fibrinogen disorders. Pathogen-reduction may be performed on plasma used for the preparation of cryoprecipitate, or on the product itself using a validated method. The residual risk of virus transmission is strongly dependent on the regional virus epidemiology and the screening technology applied. Hence, implementation of a pathogen inactivation technology for cryoprecipitate should not be a substitute for established Good Preparation Practices in donor selection, blood collection, laboratory testing for HIV, HBV and HCV and other relevant agents including emerging viruses, product processing, traceability and hemovigilance reporting, as described in WHO Recommendations and Guidelines (6, 7, 8).

In line with the recommendation of the World Federation of Hemophilia (9) locally generated pathogen-reduced cryoprecipitate should be regarded as a step-wise improvement in the treatment of patients with bleeding disorders that should not supplant and may coexist with programs to expand patient access to CFC through local or regional plasma fractionation, toll fractionation of domestic plasma, or importation of the products. Treatment with cryoprecipitate that is not pathogen-reduced should be discouraged, particularly in the setting of repeated use due to the risk of contamination with blood-borne viruses that is amplified by plasma pooling. Based on these considerations, the WHO Blood Regulators Network advocates use of pathogen-reduced cryoprecipitate in resource limited settings until CFC are available and affordable, subject to a careful assessment of risks and benefits and an organized nationally regulated blood system operating under Good Preparation Practices.

References


8. WHO. A guide to establishing a national haemovigilance system. https://apps.who.int/iris/bitstream/handle/10665/250233/9789241549844-eng.pdf?sequence=1