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World Federation of Hemophilia Statement on Cryoprecipitate for Treatment of Congenital Bleeding Disorders

Notable considerations

Cryoprecipitate is prepared by slow thawing of fresh frozen plasma (FFP) at 4^0C for 10-24 hours. It appears as an insoluble precipitate and is separated by centrifugation. Cryoprecipitate contains significant quantities of factor VIII (about 3-10 IU/ml), von Willebrand factor, fibrinogen and factor XIII but *not factor IX or factor XI*. The resultant supernatant is called cryo-poor plasma and contains other coagulation factors such as factors VII, IX, X and XI. Although cryoprecipitate has been available for 50 years and was originally developed as a therapy for patients with factor VIII deficiency (hemophilia A), it is now most commonly used to replenish fibrinogen in persons with acquired coagulopathies such as occurs with cardiac surgery, trauma, liver transplantation and catastrophic obstetrical hemorrhage. Cryoprecipitate is a pooled product that does not undergo pathogen inactivation and has been associated with adverse events including transmission of blood-borne pathogens and transfusion-related lung injury. Due to these safety concerns and the availability of alternative fibrinogen preparations, cryoprecipitate has been withdrawn from use in a number of countries. Most importantly, clotting factor concentrates (CFCs) that are either recombinantly-derived or highly purified plasma-derivatives that undergo state of the art pathogen inactivation, have supplanted cryoprecipitate for the treatment of congenital bleeding disorders. Despite this, there has been continued interest in cryoprecipitate, as it has been suggested that ultrapure clotting factor products may carry a greater risk for inhibitor development in persons with hemophilia. The incidence of inhibitors varies greatly between studies, based on not only treatment differences, but frequency of inhibitor testing, length of exposure and duration of observation. This heterogeneity between studies precludes meaningful comparison. The overall body of evidence does not appear to demonstrate a significantly lower incidence of inhibitors for cryoprecipitate compared to ultrapure factor concentrates. Thus, the unproven differences in inhibitor incidence do not diminish the concerns over the safety and efficacy of this product for the proper treatment of congenital bleeding disorders.

Decision-making process and recommendations

1. **Due to concerns about the safety and quality of cryoprecipitate, its use in the treatment of congenital bleeding disorders is *not recommended* and can only be justified in situations where CFCs are not available, as CFCs have superior safety and efficacy. When cryoprecipitate is the only product available, it is *strongly encouraged* that only virally-inactivated cryoprecipitate be used.**
2. **The manufacture of small pool, solvent/detergent-treated cryoprecipitate has been described, although this does not provide sufficient protection against non-lipid enveloped viruses. These products, though providing some added safety over untreated cryoprecipitate, *should not be regarded as a substitute for CFCs* but rather used only in the transition to CFCs where resource constraints exist.**

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