NAC STATEMENT ON FIBRINOGEN CONCENTRATE USE IN ACQUIRED HYPOFIBRINOGENEMIA

FIBRINOGEN CONCENTRATE SUBCOMMITTEE

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ABBREVIATIONS

AFP	Apheresis Frozen Plasma
FC	Fibrinogen Concentrate
FP	Frozen Plasma
NAC	National Advisory Committee on Blood and Blood Products
S/D Plasma	Solvent-Detergent Plasma

1.0 FIBRINOGEN REPLACEMENT PRODUCTS IN CANADA

Fibrinogen replacement in the setting of acquired hypofibrinogenemia plays an important role in management of massive bleeding post cardiac surgery, trauma and obstetrical hemorrhage among others. However, there continues to be a lack of evidence firmly guiding fibrinogen replacement product choice as well as ongoing uncertainties as to the optimal target and dose. Fibrinogen concentrate (FC), plasma (including frozen plasma (FP), apheresis frozen plasma (AFP), and Solvent-Detergent Plasma (S/D Plasma)), and cryoprecipitate are currently used to treat acquired hypofibrinogenemia.

There are two FC products currently available in Canada: RiaSTAP (CSL Behring) and FIBRYGA (Octapharma).[1,2] Both are licensed for treatment of acute bleeding episodes and perioperative prophylaxis in adult and pediatric patients with congenital afibrinogenemia and hypofibrinogenemia. FIBRYGA is also licensed as a complementary therapy during the management of uncontrolled severe bleeding in patients with acquired fibrinogen deficiency during surgical interventions.[2] The use of FCs in acquired hypofibrinogenemia is supported by studies, including a high-quality randomized trial in bleeding patients undergoing cardiovascular surgery.[3]

According to data provided by the manufacturers, in addition to fibrinogen, FCs contain trace amounts of the other substances, such as Factor XIII and fibronectin. These substances are not listed as active ingredients in the product monograph and the concentrations in the final product may vary. As such, their clinical relevance, if any, is unknown. Furthermore, both FCs appear to have similar efficacy in improving clot firmness in a dilutional hypofibrinogenemia model *in vitro*.[4]

The major difference between these products is related to the product storage: FIBRYGA is stored at room temperature for up to 36 months whereas RiaSTAP is stored in a refrigerator for up to 60 months.[1,2]

Plasma is indicated for replacement of multiple clotting factor deficiencies and should not be used solely for fibrinogen replacement. The plasma components available are considered equivalent in terms of clinical effectiveness. The additional risks of plasma transfusion include transfusion associated circulatory overload, transfusion related acute lung injury and allergic reactions.

Cryoprecipitate is prepared from slowly thawed FP and is indicated for replacement of fibrinogen in patients with congenital and acquired fibrinogen deficiency (quantitative or qualitative) in the setting of bleeding or an increased risk of bleeding (ex. impending major surgery).

Currently, there is no evidence of superiority of one fibrinogen replacement source over the others in terms of clinical effectiveness for the management of acquired hypofibrinogenemia. FC is pathogen inactivated and has a preferred safety profile in terms of transmissible disease risk as compared to FP and cryoprecipitate. The use of cryoprecipitate has fallen in the past decade from 2.3 per 1000 to 0.1 per 1000 population nationally exclusive of Québec.

2.0 FIBRINOGEN CONCENTRATE DOSING

Fibrinogen content of the above-mentioned products is as follows:[1,2,5-8]

- FC: 0.9-1.3 g per vial
- AFP (thawed): 3.100 +/- 0.647 g/L
- FP (thawed): 2.97 +/- 0.69 g/L
- S/D Plasma (thawed): 2.5 +/- 0.1 g/L
- Cryoprecipitate: 0.366 +/- 0.115 g per unit

Optimal dosing of the above-mentioned products is affected by:

- The inter-donor variability of fibrinogen content in blood components; and,
- Each unique patient clinical situation, including size, amount and rate of bleeding, baseline fibrinogen level, liver synthetic function and underlying diagnosis.

In a bleeding obstetrical patient with acquired hypofibrinogenemia, fibrinogen replacement is indicated when fibrinogen level is less than 2.0 g/L.[9,10] In a massively bleeding or preoperative patient with acquired hypofibrinogenemia, fibrinogen should be replaced when the level is less than 1.5 g/L.[11-13]

Options for fibrinogen replacement in adult patients with acquired hypofibrinogenemia include the following:[1,2,5-8]

- FC: 2-4 g
- FP or AFP: 3-4 units (10-15 mL/kg)
- S/D Plasma: 4-5 units (10-15 mL/kg)
- Cryoprecipitate: 10 units (1 unit/10 kg)

In neonates and pediatric patients, it is recommended to consult with the product monograph and a specialist with expertise in managing pediatric/neonatal coagulopathy prior to administration of FCs. In published studies of acquired hypofibrinogenemia in neonatal or pediatric populations, FC dosing has ranged between 30-60 mg/kg.[14,15] The smallest FC vial size available is 1 gram. In patients requiring doses smaller than 1 gram, wastage should not be a barrier to FC use in neonatal and pediatric patients.

Following administration of a fibrinogen replacement therapy, repeat bloodwork should be completed within 60 minutes to assess the degree of fibrinogen increment. The expected increment is approximately 0.5-1.0 g/L.[3,7,15]

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APPENDIX A: SUMMARY OF REVISIONS

July 2018

Section 2.0	Addition of dosing recommendations for pediatric patients. Clarified suggested fibrinogen replacement threshold for obstetrical patients.

February 2020

Section 1.0	Added discussion on RiaSTAP and FIBRYGA as two brands of fibrinogen concentrate now available from Canadian Blood Services. Added statement on fibrinogen concentrate having a favorable safety profile over cryoprecipitate or frozen plasma for fibrinogen replacement.
References	Added reference for FIBRES study.

January 2021

Document Title	Revision of document title from “NAC Statement on Fibrinogen Concentrate” to “NAC Statement on Fibrinogen Concentrate Use in Acquired Hypofibrinogenemia”.
Section 1.0	Update of fibrinogen concentration in cryoprecipitate and plasma, with new references. Clarification inserted that plasma should not solely be used for fibrinogen replacement. Added language re: licensure of FIBRYGA for acquired hypofibrinogenemia. Inserted suggested timeframe for fibrinogen level reassessment following fibrinogen replacement therapy.

February 2025

Section 1.0	Removed information regarding fresh frozen plasma. Added information regarding apheresis frozen plasma and Solvent-Detergent Plasma. Acknowledgement of the decreased use of cryoprecipitate in Canada.
Section 2.0	Removed information regarding fresh frozen plasma. Added information regarding apheresis frozen plasma and Solvent-Detergent Plasma. Acknowledgement of potential wastage due to fibrinogen concentrate vial sizes. Update to fibrinogen content in transfusable blood components, provided by Canadian Blood Services.