

# Guidelines for cryoprecipitate transfusion

A new document from the Transfusion Medicine Advisory Group describes appropriate use of cryoprecipitate plasma.

**ABSTRACT: The literature shows there is often inappropriate use of blood products, including cryoprecipitate plasma, because of inadequate education of physicians. Guidelines for cryoprecipitate transfusion have been developed by the Transfusion Medicine Advisory Group of British Columbia to educate clinicians and address transfusion practices in the province. These guidelines are based on a MEDLINE search and consultation with hematopathologists and clinicians. At present, transfusion of cryoprecipitate is indicated for hypofibrinogenemia/dysfibrinogenemia, von Willebrand disease, hemophilia A, factor XIII deficiency, and management of bleeding related to thrombolytic therapy. Cryoprecipitate should not be used to prepare fibrin glue or to treat sepsis.**

**T**he Transfusion Medicine Advisory Group (TMAG) of BC has prepared guidelines to provide physicians with current information on the appropriate use of cryoprecipitate plasma. These guidelines are available electronically on the British Columbia Provincial Coordinating Office web site ([www.bloodlink.bc.ca](http://www.bloodlink.bc.ca)) and will be updated periodically. Prescribing physicians are responsible for referring to the most recent guidelines.

## How the guidelines were developed

These guidelines were developed to direct therapy but are not intended as a rigid prescription for cryoprecipitate use. The guidelines are based on a MEDLINE search using the key words “cryoprecipitate” plus “trials” or “randomized” or “guidelines” or “reviews.” The levels of evidence and grades of recommendations are based on standards developed by the US Agency for Healthcare Research and Quality (formerly the US Agency for Health Care Policy and Research)<sup>1</sup> (see Appendix A). Because of the limited number of clinical trials completed, most of the recommendations are based on expert opinion—level IV evidence, grade C recommendation. These guidelines were reviewed by hematopathologists and clinicians, including hema-

tologists and critical care physicians, and were subsequently approved by the Transfusion Medicine Advisory Group (see Appendix B).

## General considerations

Physicians contemplating the use of cryoprecipitate (see **Table**), should keep in mind the following general considerations:

- In British Columbia, informed consent is required for the transfusion of cryoprecipitate.
- All routine coagulation parameters

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should be checked before ordering cryoprecipitate. This includes complete blood count (CBC), platelet count, international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen.

- The Transfusion Medicine Laboratory Service should be made aware of the clinical diagnosis on the request form used to order cryoprecipitate. The reason for the transfusion should also be clearly and accurately recorded in the patient's chart, and in any documentation that is used when administering cryoprecipitate.
- Cryoprecipitate should be given only after risks associated with transfusion of allogeneic blood products have been considered and only when the benefits outweigh the risks.
- Alternative treatments or adjunctive agents should be used to minimize or to avoid the use of cryoprecipitate. For example, desmopressin (DDAVP), Humate P, fibrinogen concentrates, and antifibrinolytic agents may be appropriate in specific situations.
- Most laboratories in British Columbia convert the prothrombin time (PT) to the international normalized ratio to facilitate comparison of results between laboratories. (Throughout the document, we have tried to use the INR where possible, as this is typically what is reported by laboratories.)

### Clinical indications for use of cryoprecipitate

Clinical experience supports the use of cryoprecipitate in the following situations.

**Hypodysfibrinogenemia.** Reduced levels of fibrinogen activity can result from either a functional or qualitative defect (dysfibrinogenemia) or a quantitative deficiency, as is seen in massive transfusion or disseminated intravascular coagulation (DIC). Transfusion ther-

apy with either frozen plasma (FP) or cryoprecipitate is usually indicated if fibrinogen levels are less than 1.0 g/L, and bleeding is present, although clinically significant bleeding can occur at higher levels. If fibrinogen levels are greater than 1.0 g/L in the setting of active bleeding secondary to DIC, then FP should be given instead of cryoprecipitate in order to address the multiple factor deficiencies typical of DIC. Cryoprecipitate may be considered as a substitute for FP when the required volume of plasma is relatively contraindicated and targeted fibrinogen replacement in a small volume is desirable.<sup>2,4</sup> (Level IV evidence, grade C recommendation.)

**von Willebrand (vWD) disease and hemophilia A (HA).** The current practice in patients with mild (type 1) vWD disease or mild HA is to use desmopressin and/or antifibrinolytics or virus-inactivated factor VIII (F VIII) concentrate (e.g., Humate P), which contains both F VIII:C and von Willebrand factor multimers. Most hemophilia patients with F VIII:C deficiency are treated with F VIII:C concentrate, which is now a recombinant product and no longer derived from human plasma. Cryoprecipitate can be used by patients with vWD disease that is unresponsive to desmopressin and by hemophilia A patients in those locations where F VIII:C concentrates are not available. Every effort must be made to obtain the preferred recombinant factor concentrate for hemophiliacs before resorting to the use of cryoprecipitate.<sup>2,6</sup>

#### Dosing:

- vWD disease (as a second-line therapy—see above)

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Adult: 10 to 12 units (bags) every 12 hours

Child: 1 unit (bag) per 6 kg of body weight every 12 hours

- Hemophilia A (only as a second-line therapy—see above) (Level IV evidence, grade C recommendation.)

**F XIII deficiency.** Hereditary deficiency of factor XIII is an extremely rare condition. In 2006, the Canadian Hemophilia Registry ([www.fhs.mc-master.ca/chr/2006](http://www.fhs.mc-master.ca/chr/2006)) identified only 41 cases. Hemostasis may be achieved with levels as low as 2% to 3%. Compared with the half-life of other coagulation factors, the half-life of F XIII is very long (9 to 10 days). Plasma-derived F XIII concentrate (Fibrogammin P) is licensed and available in Canada through the Special Access Programme for use in patients with F XIII deficiency, but is not stocked in all regional blood centres. Because of the rarity of F XIII deficiency, specific factor concentrate is usually not readily available in emergent situations, and it is in these situations that cryoprecipitate can and should be used.<sup>7</sup>

#### Dosing:

- 1 unit (bag) per 10 kg of body weight every 7 to 14 days (Level IV evidence, grade C recommendation.)

**Management of bleeding related to thrombolytic therapy.** Cryoprecipitate can be used to manage intracranial bleeding in patients during or after administration of tissue plasminogen activator (tPA).<sup>8</sup> Randomized controlled clinical trials of cryoprecipitate

$$\text{number of bags of cryoprecipitate} = \frac{[(\text{plasma volume in mL} \times \% \text{ increase in F VIII:C needed})/100]}{80}$$

**Table. Characteristics of four frozen plasma products.**

	<b>Frozen plasma</b> (from whole blood collection)	<b>Fresh-frozen plasma</b> (from apheresis collection)	<b>Cryoprecipitate plasma</b> (cryo)	<b>Cryosupernatant plasma</b> (cryo-poor plasma)
<b>Preparation</b>	<p>Whole blood is centrifuged at high speed, allowing separation of plasma, red blood cells (RBCs), and the buffy coat layer (platelets, white blood cells, some RBCs and plasma). Plasma is frozen within 24 hours of collection and is designated as frozen plasma (FP). It is prepared for use by thawing at 37°C, a process that can take up to 30 minutes.</p> <p>Once thawed, the product should be transfused immediately, with completion of transfusion within 4 hours of issuing product.</p>	<p>Whole blood is processed through a cell separator to obtain plasma. Plasma is frozen within 8 hours of collection and is designated as fresh-frozen plasma (FFP). In general, 1 unit of FFP from apheresis collection is equivalent to approximately 2 units of FP from whole blood collection. The two products can be used interchangeably.</p> <p>Once thawed, the product should be transfused immediately, with completion of transfusion within 4 hours of issuing product.</p>	<p>Plasma is frozen for 24 hours, and then thawed at 1°–6°C until insoluble proteins precipitate. The pack is centrifuged to obtain the cryoprecipitate. The cryoprecipitate is then refrozen for storage.</p> <p>Once thawed, the product should be transfused immediately, with completion of transfusion within 4 hours of issuing product.</p>	<p>Plasma is frozen for 24 hours, and then thawed at 1°–6°C until insoluble proteins precipitate. The pack is centrifuged to obtain the supernatant. The supernatant, or cryo-poor plasma, is then refrozen for storage.</p> <p>Once thawed, the product should be transfused immediately, with completion of transfusion within 4 hours of issuing product.</p>
<b>Factors</b>	<p>Contains all of the coagulation factors, including the labile factors (FV and FVIII:C). For product prepared within 24 hours of collection, FVIII:C levels are less than those found in fresh-frozen plasma prepared within 8 hours of collection, but levels are still at or above 0.50 IU/mL. FP can be used for coagulation factor replacement except for isolated or severe FVIII deficiency.</p>	<p>Contains all of the coagulation factors, including the labile factors (FV and FVIII:C).</p>	<p>Contains FVIII:C, von Willebrand factor (vWF), fibrinogen, FXIII, and fibronectin. Cryoprecipitate has the following factor activities: 91 IU of FVIII: C per bag, 113 IU of vWF per bag, and 150 mg of fibrinogen per bag.</p>	<p>Is deficient in high molecular weight vWF multimers and FVIII:C.</p>
<b>Volume</b>	Each bag = 1 unit (200–250 mL)	Each bag = 1 unit (100–600 mL)	Each bag = 1 unit (5–15 mL)	Each bag = 1 unit (>100 mL)
<b>Dose</b>	<p>Typical adult dose of plasma is 10–15 mL/kg body weight.</p> <p>The pediatric dose of plasma is 10–15 mL/kg body weight.</p> <p>Infusion rate is over 2–3 hours, or as required.</p> <p>Will raise factor levels by 25%, assuming there is no ongoing consumption/loss of factors.</p>	<p>Typical adult dose of plasma is 10–15 mL/kg body weight.</p> <p>The pediatric dose of plasma is 10–15 mL/kg body weight.</p> <p>Infusion rate is over 2–3 hours, or as required.</p> <p>Will raise factor levels by 25%, assuming there is no ongoing consumption/loss of factors.</p>	<p>Typical adult dose of cryo is 1 unit/5 kg body weight, up to a total dose of 10 units (bags).</p> <p>The pediatric dose is 1 unit/5–10 kg body weight or 5–10 mL/kg.</p> <p>Will raise fibrinogen by 0.5 g/L, assuming there is no ongoing consumption/loss of fibrinogen.</p>	<p>Typically 1.0–1.5 times plasma volume exchange is performed per plasma exchange (PLEX) run.</p> <p>Indicated as replacement fluid in PLEX for thrombotic thrombocytopenic purpura.</p>

versus placebo for treatment of tPA-related bleeding are not available. However, various guidelines as well as articles in peer-reviewed journals suggest using the following clinical algorithm:

- Discontinue tPA administration with the onset of signs or symptoms of intracranial hemorrhage.
- Order stat lab studies: INR, PTT, platelet count, fibrinogen level.
- Consider administration of 10 units (bags) of cryoprecipitate.
- Consider administration of platelet concentrate if a drug-induced (e.g., ASA-induced) platelet dysfunction is likely.
- Consider neurosurgical evaluation.<sup>9</sup> (Level IV evidence, grade C recommendation.)

### Inappropriate uses for cryoprecipitate

The use of cryoprecipitate is not recommended in the following situations.

**Fibrin glue.** Allogeneic or autologous cryoprecipitate has been used to prepare fibrin glue.<sup>10,11</sup> To make this hemostatic product, cryoprecipitate is mixed with a commercial source of thrombin (usually bovine thrombin). Homemade fibrin sealants have used bovine thrombin preparations that contain bovine F V. A number of patients have developed antibodies to the bovine F V, resulting in potentially serious clinical sequelae whose management may be confounded by erroneous results in laboratory tests of coagulation.<sup>12</sup> To avoid this complication, the use of commercially manufactured fibrin sealant preparations containing human thrombin (e.g., Tisseel) is preferred.

(Level III and IV evidence, grade B and C recommendation.)

**Sepsis.** Cryoprecipitate has been used in septic patients to replace fibro-

nectin.<sup>13</sup> Fibronectin is thought to function as the major opsonin for macrophage clearance of circulating noncellular debris. In early, uncontrolled studies, infusion of cryoprecipitate in critically ill septic patients resulted in improved renal and pulmonary function and changes in peripheral hemodynamics. However, subsequent controlled studies failed to confirm any benefit.<sup>14</sup> (Level IV evidence, grade A recommendation.)

### Competing interests

None declared.

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## Appendix A

US Agency for Healthcare Policy and Research guidelines for defining the types of evidence and the grading recommendations.

### Levels of evidence

- Ia Evidence obtained from the meta-analysis of randomized controlled trials.
- Ib Evidence obtained from at least one randomized controlled trial.
- IIa Evidence obtained from at least one well-designed controlled study without randomization.
- IIb Evidence obtained from at least one other type of well-designed quasi-experimental study.
- III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
- IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

### Grades of recommendations

- A Required at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendations (evidence levels Ia, Ib).
- B Requires availability of well-conducted clinical studies but no randomized clinical trials on the topic of recommendations (evidence levels IIa, IIb, III).
- C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality (evidence level IV).

## Appendix B

The Transfusion Medical Advisory Group advises the BC Ministry of Health. It is composed of transfusion medicine experts who meet regularly to discuss pertinent transfusion-related issues and to endorse transfusion initiatives that will improve the Canadian health care system.

### Members

- Ms Sheila Armstrong, Administrator, Provincial Laboratory Coordinating Office
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