

## Rationalizing the clinical use of frozen plasma

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**R**ecognition of serious deficiencies in blood transfusion practices has led to greater scrutiny of transfusion medicine. Increasing attention is being paid not only to safety in the acquisition and processing of blood components, but also to the appropriateness of clinical transfusion practices and indications. Although there has been much careful assessment of the clinical use of red blood cells and platelets, less assiduous attention has been paid to the use of frozen plasma.

Guidelines for the clinical use of frozen plasma have been published by several organizations, including the Canadian Medical Association.<sup>1</sup> They are similar in their recommendations and are based largely on evidence from observational studies and expert opinion. This evidence indicates that frozen plasma is not substantially or consistently effective in many of the clinical contexts in which it is used, particularly for preventing or reducing bleeding associated with invasive procedures.

We have compiled broad categories of appropriate and inappropriate indications for use of frozen plasma (Box 1) from critical reviews<sup>2</sup> and various published guidelines.<sup>1,3,4</sup> Frozen plasma is usually prescribed to correct coagulopathy from various causes, as identified from laboratory test results, with or without bleeding or expected invasive procedures. However, there is little evidence to support the efficacy of frozen plasma in these circumstances or to define criteria for the degree of coagulopathy required before any benefit can be expected.<sup>2</sup> Coagulation screening assays have little value in predicting bleeding associated with invasive procedures in patients with mild to moderate coagulopathy<sup>5</sup> (international normalized ratio 1.5–3.0), and transfusion of frozen plasma has a negligible effect on correcting trivial coagulation abnormalities (international normalized ratio < 1.5).<sup>6</sup> The dose of frozen plasma required to effect major reductions in substantially prolonged clotting times is considerable (15–20 mL/kg)<sup>7</sup> and poses a risk of circulatory overload.

For resuscitation and massive transfusion, the proportion of frozen plasma used in relation to transfusions of red blood cells that provides the optimal balance between risk and benefit is highly controversial<sup>8</sup> and needs controlled study.

Two recent studies in Canada found that 45.0% and 47.6% of audited frozen plasma transfusions represented inappropriate use,<sup>9,10</sup> according to published guidelines.<sup>1</sup> The most common inappropriate use was in patients where there was no bleeding and laboratory coagulation test results were abnormal.

As a benchmark, consumption of red blood cells has been compared with contemporaneous consumption of plasma, on the basis that practices for red blood cell transfusion have

### Key points

- Much of the clinical use of frozen plasma lacks objective evidence to support its value, especially in correcting trivial abnormalities in coagulation function in patients in whom there is no bleeding.
- Transfusion practices often do not comply with practice guidelines, which themselves lack adequate evidence.
- Frozen plasma contributes significantly to the morbidity and mortality resulting from transfusion of blood components.

clearer evidence-based clinical indications and are likely to be more uniform and comparable between jurisdictions. In eight countries, the plasma to red blood cell consumption ratio varied between 0.14 and 0.31.<sup>11</sup> In Canada, the ratio varies among provinces (0.20–0.32); in one province, the ratio varied between 0.11 and 0.71 among medium-sized and large hospitals (I. Mumford. Canadian Blood Services, Ottawa, Ont.: personal communication, 2008).

Some programs such as plasma exchange may skew these figures, but they are few and will have little influence on the larger picture. Thus, it is difficult to see how truly evidence-based prescribing practices could be consistent with such variability. The evidence suggests that prescribers' perceptions of clinical indications for using frozen plasma are far from uniform. Not only do audits of frozen plasma transfusion show frequent failure to conform to published guidelines, but also the guidelines themselves are not based on convincing evidence of efficacy. There are many reasons to suppose that there is widespread use of frozen plasma for questionable clinical indications.

In addition, transfusion of frozen plasma carries risks, particularly acute lung injury and circulatory overload. Data on adverse outcomes derived from hemovigilance programs are fragmentary and likely underestimate incidence because reporting is often voluntary. Plasma is the most frequently implicated cause of transfusion-related acute lung injury; the true incidence is unknown, but it has been estimated to be between 1 in 1323 and 1 in 5000 transfusions, which includes a small but substantial proportion of fatal cases.<sup>12</sup> The decision in many countries (including Canada) to use only plasma

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**Box 1: Appropriate and inappropriate indications for use of frozen plasma****Appropriate**

- hemorrhage from coagulopathy of liver disease or disseminated intravascular coagulation
- dilutional coagulopathy of massive transfusion
- coagulation defect of liver disease or disseminated intravascular coagulation in expectation of an invasive procedure
- emergency reversal of the effect of a vitamin K antagonist in the absence of prothrombin complex concentrate
- plasma exchange for thrombotic thrombocytopenic purpura

**Inappropriate**

- elevated international normalized ratio or partial thromboplastin time in the absence of bleeding or invasive procedure
- non-urgent reversal of the effect of a vitamin K antagonist
- volume replacement
- reversal of coagulopathy from anticoagulants (e.g., heparin)
- nutrition supplement

from male donors (because plasma from parous females is more likely to provoke lung injury mediated by leukocyte antibodies induced through pregnancy) seems to reduce the incidence of this complication. Transfusion-associated circulatory overload can result from the large volume of frozen plasma required to transfer adequate amounts of coagulation factors for any discernable clinical (or laboratory) benefit. The true incidence is probably substantially under-reported, but it may be as high as 1 per 100 transfusion episodes in the elderly.<sup>13</sup> Microbial transmission and severe anaphylaxis, although uncommon complications of transfusion of frozen plasma, are sometimes fatal.

Several steps could be introduced without delay to improve the use of frozen plasma. First, where possible, vitamin K or prothrombin complex concentrate should be used instead of frozen plasma to reverse warfarin anticoagulation or treat severe vitamin K deficiency in the presence of bleeding or before emergency surgery.<sup>14</sup> Second, computer-based order entry systems could require information on the indication for frozen plasma transfusion before the order is met, and would permit prospective screening of orders for frozen plasma by transfusion medicine staff. Third, frozen plasma should not be used for volume or nutrition replacement nor to correct coagulopathy from anticoagulants (e.g., heparin or low-molecular-weight heparin) when there is no expected benefit.

Over the longer term, evidence-based prescribing practices must be improved. Randomized controlled clinical trials are

needed to establish the appropriate types of coagulopathy and the levels at which to transfuse frozen plasma to treat bleeding or to prepare for an invasive procedure in patients at risk. Such trials could also be designed to determine the efficacy and hazards of using prothrombin complex concentrate. More clinical trials are needed to determine the appropriate amount of frozen plasma to be incorporated into protocols for “massive” transfusion. Large retrospective audits of the appropriateness of frozen plasma transfusion across different jurisdictions could help hospitals with the highest levels of inappropriate use improve practice through feedback to clinicians and transfusion committees.

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