

Frozen Plasma/Prothrombin Complex Concentrate Toolkit

Prepared by



**Central
ORBCoN Office**
416.480.6100 ext. 89433

**Northern and Eastern
ORBCoN Office**
613.798.5555 ext. 19741

**Southwest
ORBCoN Office**
905.525.9140 ext. 22915

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Choosing Wisely Canada Recommendations



The **Choosing Wisely Canada** (CWC) campaign seeks to promote avoidance of wasteful or unnecessary tests, treatments and procedures. An increasing weight of evidence from clinical trials is accumulating to support the clinical benefits of restrictive rather than liberal transfusion policies. The following are CWC recommendations specifically related to frozen plasma and prothrombin complex concentrates.

Don't transfuse plasma to correct a mildly elevated (<1.8) international normalized ratio (INR) or activated partial thromboplastin time (aPTT) before a procedure.

A mildly elevated INR is not predictive of an increased risk of bleeding. Furthermore, transfusion of plasma has not been demonstrated to significantly change the INR value when the INR was only minimally elevated (<1.8).

Don't routinely use plasma or prothrombin complex concentrates for nonemergent reversal of vitamin K antagonists.

Patients requiring non-emergent reversal of warfarin can often be treated with vitamin K or by discontinuing the warfarin therapy. Prothrombin complex concentrates should only be used for patients with serious bleeding or for those who need urgent surgery. Plasma should only be used in this setting if prothrombin complex concentrates are not available or contraindicated.

Don't routinely use blood products to reverse warfarin

Patients requiring reversal of warfarin can often be reversed with vitamin K alone. Prothrombin complex concentrates or plasma should only be used for patients with serious bleeding or requiring emergency surgery.

For additional information on the Choosing Wisely Canada campaign and its associated recommendations visit: www.choosingwiselycanada.org

Introduction

In 2008 and 2013, audits of Frozen Plasma (FP) use in Ontario were undertaken to determine the then current ordering and clinical utilization practices of Ontario physicians, and to establish whether recommendations for improvement in practice arising from the 2008 audit had influenced utilization.

In the 2008 audit, of 573 requests for FP, 54.8% were appropriate, 28.6% were inappropriate and 16.6% were indeterminate primarily due to lack of peri-transfusion laboratory coagulation testing. (www.transfusionontario.org; Tinmouth et al., 2013). In the 2013 audit, the introduction of 4-factor Prothrombin Complex Concentrates (PCCs) in late 2008 had substantially influenced the clinical prescribing of FP and, consequently, the 2013 audit included both FP and PCCs. Criteria for the appropriateness of FP use were accordingly modified to recognize specific changes in practice resulting from the introduction of PCCs. Of the 322 orders for FP included in the 2013 audit (excluding those for plasma exchange), 42.2% were appropriate, 51.9% were inappropriate and 5.9% were indeterminate.

Thus, in spite of the promulgation of guidelines and recommendations for improvement in clinical transfusion practice, and apart from considerable replacement of FP with PCCs for urgent warfarin reversal, widespread inappropriate and unnecessary transfusion of FP continues.

As a consequence of the introduction of PCCs, advances in the understanding of the value and hazards of the use of Frozen Plasma, and recognizing the continuing provincial use of FP outside of guidelines, this toolkit has been revised to reflect these factors.

This toolkit is designed to provide hospital Transfusion Services with the tools required to optimize the use of FP. It also provides a summary of recommendations for the use of alternatives to FP, including Vitamin K and PCCs. (National Advisory Committee on Blood and Blood Products. Recommendations for the use of prothrombin complex concentrations in Canada. May 16, 2014. www.nacblood.ca/resources/guidelines)

The ORBCoN FP/PCC toolkit includes

1. The Ontario Clinical Practice Recommendations for the Use of Frozen Plasma (FP)
2. Ontario Frozen Plasma Recommendations-Supporting documentation
3. Algorithm for Screening Frozen Plasma Orders (with and without anticoagulants)
4. Ontario Frozen Plasma Recommendations Algorithm - Guidance Document
5. Guidance for Use of Prothrombin Complex Concentrates (PCCs)
6. References

An electronic audit tool for FP utilization is available in the ORBCoN etools application. <http://etools.transfusionontario.org/> If you do not have access to the ORBCoN etools application please contact your Regional ORBCoN office.

The Ontario Clinical Practice Recommendations for the Use of Frozen Plasma (FP)

Situations in which the transfusion of FP is reasonable:

Clinical Indication	Reason
Bleeding	Liver disease or DIC with INR 1.8 or greater
	Massive transfusion (expect more than 10 RBC units transfused in 24 hours) with INR 1.8 or greater (or rapidity of bleeding does not allow for MD to wait for results, usually transfusion rate in excess of 4 RBC units per hour)
	Inherited or acquired single factor deficiencies where specific factor concentrate is unavailable
Surgery or major procedure	Liver disease, dilutional coagulopathy or DIC with at least INR 1.8 or greater
	Inherited or acquired single factor deficiencies where specific factor concentrate is unavailable
Plasma exchange	Thrombotic thrombocytopenic purpura (TTP)

Situations in which transfusion of FP is **NOT** useful:

- INR less than 1.8 (including major surgery or non-life-threatening bleeding)*
- Use of 1:1 or 2:1 (RBC:FP) replacement when patient is unlikely to require massive transfusion
- Coagulopathy in the absence of bleeding or need for major emergency surgery
- Minor procedures with any elevation in the INR*
- Elective reversal of warfarin where time allows for warfarin cessation and/or use of vitamin K
- Reversal of anticoagulants (heparin/LMWH, rivaroxaban, dabigatran, apixaban)**
- Volume expansion or “nutrition support”

* *Note: Patients with an increased INR do not have an increased risk of bleeding with minor procedures and there is no evidence that transfusing plasma will prevent or reduce bleeding. (Paracentesis, thoracentesis, central line insertion, PICC, bone marrow aspiration/biopsy)*

** *Note: FP has no effect in reversing or neutralizing heparins or thrombin inhibitors: FP should ONLY be used for warfarin reversal if PCCs are not available.*

Note: Clinical Practice Recommendations for the use of FP and an order set template can be found at www.transfusionontario.org

Most Common Inappropriate Uses of Frozen Plasma from Provincial Audit

Background

The use of FP is declining, partly as a consequence of the introduction of PCCs. Recognition of the limitations in the clinical effectiveness of FP in managing minor abnormalities of coagulation function, and increasing awareness of the potential hazards of FP transfusion should lead to declining use. In particular, the frequency of, and morbidity and mortality from, Transfusion Associated Circulatory Overload (TACO) is being increasingly recognized especially in the elderly and those with significant co-morbidities (Narick et al. 2012; Murphy et al., 2013; Clifford et al., 2017). Thus, we have compelling reasons to avoid FP transfusion without good clinical evidence that benefit outweighs risk.

However, in spite of these factors and the promulgation of guidelines and transfusion management recommendations, inappropriate use of FP continues to be a problem in Ontario, as confirmed by the 2013 audit. Parenthetically, this is a worldwide problem (Ref. Appendix B, 2013 audit report, www.transfusionontario.org) but that does not exempt us from the responsibility for improvement.

The summary of inappropriate uses in the provincial audit and recommendations in this toolkit are intended to assist individual hospital Transfusion Services and Transfusion Committees in implementing measures to reduce inappropriate and unnecessary FP transfusions, including the appropriate and timely use of alternatives such as PCCs and Vitamin K.

Most Common Inappropriate Uses of FP

1. Reversal of warfarin or vitamin K deficiency in the absence of bleeding or urgent major invasive procedure (within 6 hours)

- FP is NOT indicated if the patient is not bleeding or does not require an emergency invasive procedure or surgery.
- If reversal is required for bleeding or for an emergency invasive procedure or surgery, transfusion of FP is ONLY justifiable if PCCs are not available in time. **All hospitals should stock 3000 IU of PCC and if not used before expiration date, redistribute through the Provincial Redistribution program.**

2. Treatment for trivial abnormalities of laboratory test results that are not associated with an increased risk of bleeding

- The Canadian Society for Transfusion Medicine and the Choosing Wisely Canada campaign recommend an INR of 1.8 as the “cut-off” for deciding on transfusion of FP to correct coagulopathy associated with liver disease, replacing the historic recommendation of 1.5. (www.choosingwiselycanada.org)
- FP transfusion to reverse elevations of INR in preparation for minor procedures (e.g. insertion of central venous catheter) is not useful and may result in more adverse outcomes (Segal and Dzik, 2005; Haas et al., 2011; Callum and Dzik, 2011; Muller et al., 2015)
- FP is ineffectual in decreasing a minimally elevated INR (Holland and Brooks, 2006; Abdel-Wahab et al., 2006; Karam et al., 2015).

3. Reversal of coagulation defect with elevated INR in the absence of bleeding or urgent invasive procedure

- FP is not indicated if the patient is not bleeding or does not require an emergency (within 6 hours) invasive procedure or surgery.
- Patients with liver disease have balanced reduction in pro-coagulant and anticoagulant factors (proteins C and S), and preserved thrombin generation (Lisman and Porte, 2010; Callum et al., 2018), and often do not require correction of an elevated INR even before procedures.

4. Heparin reversal

- FP is ineffective in reversing the effect of heparin agents. Specific antidotes are available to neutralize unfractionated heparin (e.g. protamine).
- FP contains anti-thrombin which could exacerbate the anticoagulant effect of heparin.

5. Summary of measures for rapid reversal of anticoagulant therapy

Drug	Antidote
Warfarin	PCC at 1000 IU each over 5min INR<3 – 1000 INR 3-5 – 2000 INR >5 – 3000 INR unknown – 2000
Dabigatran	Idarucizumab 5 grams over 10 min
Apixaban*	PCC 2000 IU (repeat in 1 hour if bleeding continues) – Note: this is off-label use of the product and unproven effectiveness.
Rivaroxaban*	PCC 2000 IU (repeat in 1 hour if bleeding continues) – Note: this is off-label use of the product and unproven effectiveness.
LMWH	Protamine (consult local pharmacy for recommendations)
Heparin	Protamine (consult local pharmacy for recommendations)

*For further detail, see under “Guidance for use of Prothrombin Complex Concentrates” below.

Audit of Prothrombin Complex Concentrates (PCCs) 2013, Principal Findings

1. All audit participating hospitals indicated they had guidelines for the use of PCCs.
2. 113 orders for PCCs were evaluated during the audit. Orders were deemed appropriate in 70%, inappropriate in 28% and indeterminate in 2%.
3. The reasons for inappropriate classification were:
 - Reversal of warfarin effect or vitamin K deficiency in absence of bleeding or urgent invasive procedure.
 - Reversal of coagulopathy other than warfarin, vitamin K deficiency or congenital deficiency of factors II, VII, IX or X, regardless of bleeding status or procedure.
 - Warfarin effect but INR <1.5 and no bleeding.
4. Using INR dose determination as the only criterion for appropriateness of dosage (body weight data not collected), dose was appropriate in at least half of the orders audited. Target INR of 1.5 was achieved in about 80% of recipients.
5. Of patients treated for warfarin reversal, 59% received PCCs alone, 35% received FP alone and 6% received both.

NB. Treatment with FP is only necessary when treating life-threatening major bleeding leading to dilutional or trauma-associated coagulopathy.

Guidance for Use of Prothrombin Complex Concentrates (PCCs)

Hospital policy and procedures should be developed based on the most recent guidelines issued by the National Advisory Committee on Blood and Blood Products. (www.nacblood.ca May 2014)

1. Two PCC products are available and approved for use in Canada - Octaplex[®] and Beriplex[®].
2. Recommended for reversal of warfarin therapy or Vitamin K deficiency in patients (INR 1.5 or greater):
 - Exhibiting major bleeding manifestations.
 - Requiring urgent (less than 6 hours) surgical procedures (note: the 6 hour limit refers to the duration of effectiveness of treatment due to the short biological half-life of critical coagulation factors).
 - Reversal in the absence of major bleeding or urgent surgery may be achieved with Vitamin K alone.
 - Supplemental Vitamin K (5-10 mg IV) should be co-administered or else re-bound anticoagulant effect will occur at 6 hours. Note: administration of vitamin K does not lead to an inability to re-anticoagulant patients.
3. Contraindicated in patients with a history of heparin induced thrombocytopenia (due to heparin content of PCC product).
4. PCCs are NOT recommended for:
 - Effective reversal of oral anticoagulant warfarin therapy prior to minor invasive procedures e.g. insertion of a central venous line, thoracentesis (often warfarin therapy does not need interruption, or warfarin can be held and/or IV vitamin K administered alone).
 - Treatment of elevated INRs without bleeding or urgent surgical interventions.
 - Coagulopathy of liver disease.
 - Patients with recent history of thrombo-embolic disease.(within the past 3 months)
5. For special patient populations (pregnancy, pediatrics, congenital deficiency of Factors II and X, direct oral anticoagulant agents) refer to National Advisory Committee on Blood and Blood Product Guidelines.

Dose: Dosage may be based on INR alone or using both INR and body weight.

For INR alone the recommended dose schedule is located at the following NAC link:
<http://www.nacblood.ca/resources/guidelines/PCC-Recommendations-Final-2014-05-16.pdf>

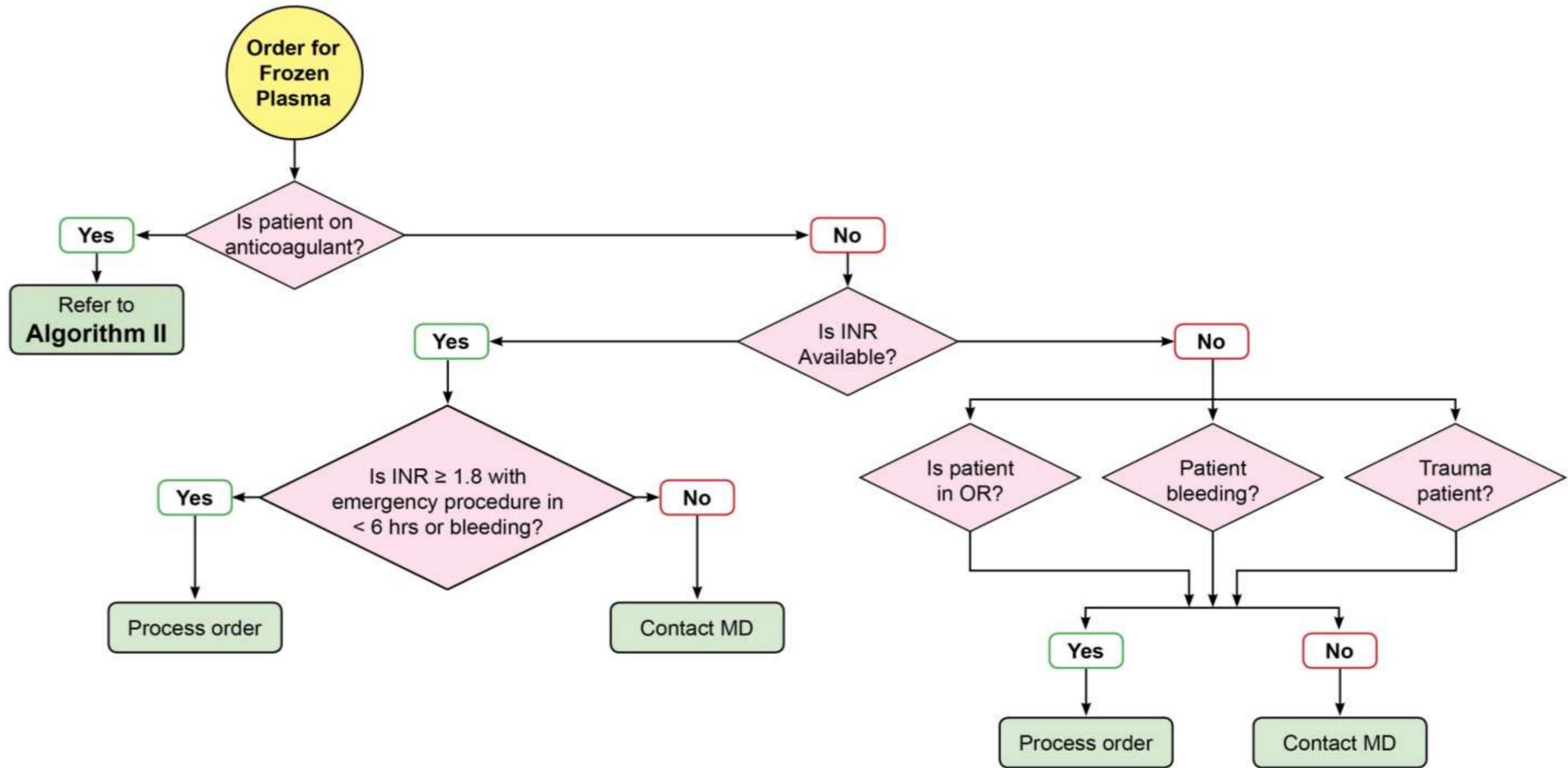
The dose schedule based on combined criteria of INR and weight is more complex and reference should also be made to the NAC Guidelines link provided above.

6. At present, there is no specific antidote to factor Xa inhibitors approved for use in Canada (apixaban, rivaroxaban). However, a recent cohort study using PCCs to treat serious hemorrhagic complications of factor Xa anticoagulation has demonstrated clinical effectiveness with a low rate of thromboembolic complications. Clearly, the evidence is encouraging but preliminary and requires examination through formal randomized, controlled clinical trials.

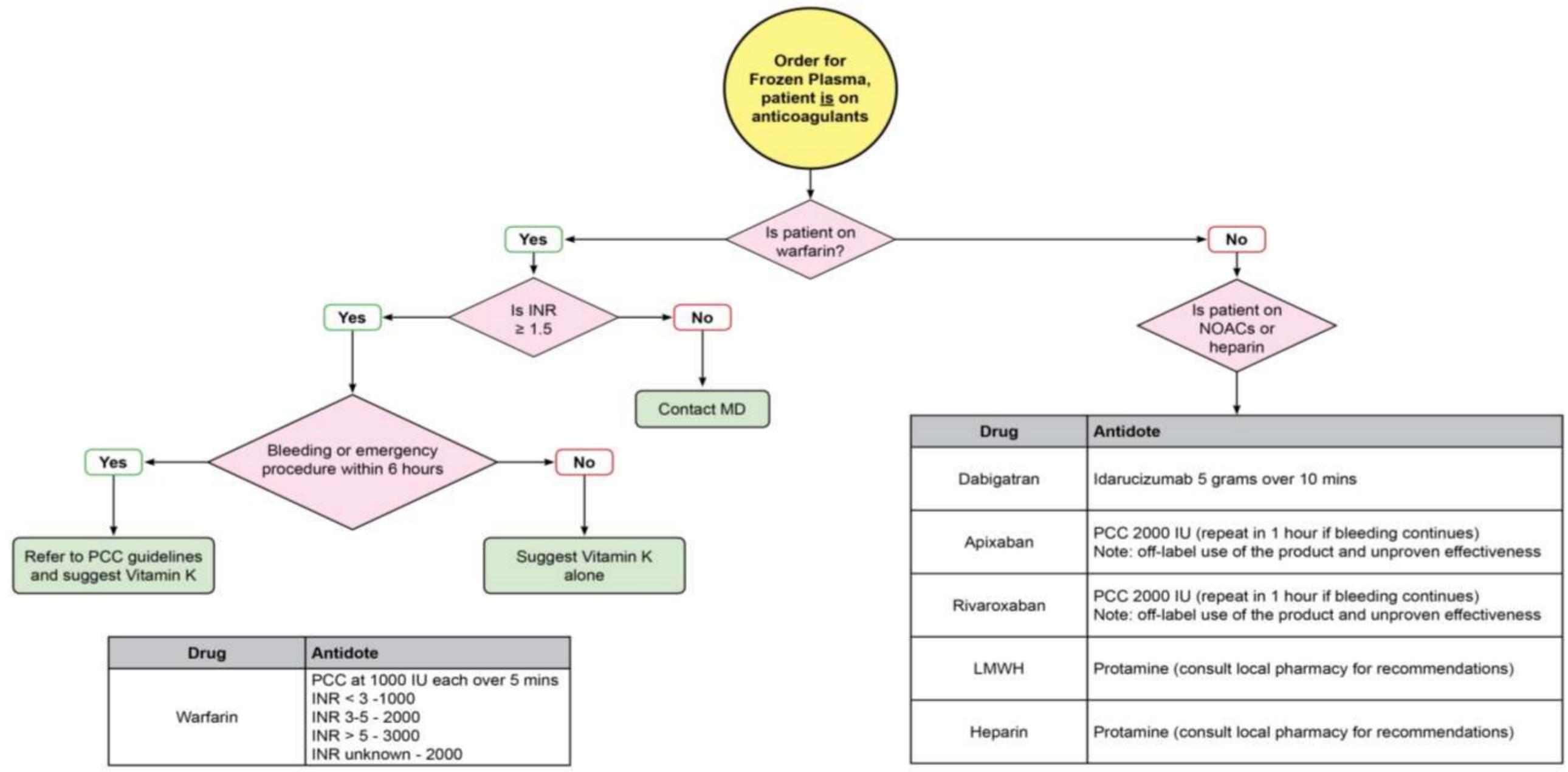
The dosage schedule employed was 1,500IU for patients weighing <65Kg and 2,000IU for patients weighing 65Kg or more. In a small minority of patients a further dose of 500-1,000IU was given if the effect of the first dose proved insufficient. (Majeed et al., 2017).

PCCs are not recommended for reversal of dabigatran (see algorithm II, p.11)

Algorithm I: Screening Frozen Plasma Orders



Algorithm II: For Screening Frozen Plasma Orders (patient on anticoagulants)



N.B Frozen plasma transfusion is no longer regarded as appropriate treatments for reversal of anticoagulant effect.

Ontario Frozen Plasma Recommendations Algorithm – Guidance Document

The Ontario Provincial Frozen Plasma Audits conducted in 2008 and 2013 both demonstrated that about half of the orders for FP were deemed either "inappropriate" or "indeterminate" (i.e. the complete lack of testing pre-transfusion or post-transfusion did not permit determination of appropriateness). This algorithm was designed to assist in reducing unnecessary FP transfusions by guiding ordering physicians, medical directors of Transfusion Services and Medical Laboratory Technologists in prospectively or retrospectively reviewing or auditing orders for FP, to support the rational clinical use of FP in accordance with recognized practice guidelines. Current evidence supports the change in threshold INR from "greater than 1.5" to "equal to or greater than 1.8" (Holland and Brooks, 2006; Abdel-Wahab et al., 2006; Szczepiorkowski ZM and Dunbar NM, 2013: www.transfusion.ca/Education/Choosing-Wisely) other than in the rare case where, in the absence of PCCs, FP is required for reversal of warfarin effect in the face of major bleeding or in support of an urgent major surgical procedure (Callum et al., 2016).

Implementation of guidelines should include feedback on performance either to individual physicians or the system in general. Auditing Frozen Plasma use is one mechanism that can be used to collect and analyze utilization patterns.

Caveats to the use of the Frozen Plasma algorithm:

1. The algorithm does not address the use of Frozen Plasma for plasmapheresis. It is assumed that plasmapheresis would be undertaken following consultation with a Hematologist since it is a treatment that occurs in centres that specialize in managing a relatively small and selected patient population.
2. The algorithm does not provide information related to appropriate dosing for Frozen Plasma or Vitamin K or Prothrombin Complex Concentrates. The results of the Ontario Provincial Frozen Plasma Audit indicate that there appears to be a trend toward "under-dosing" for Frozen Plasma requests.

Recommended dosing:

Plasma: 10 – 15mL/kg or
3 units for a small adult,
4 units for a large adult.

Vitamin K: Dose and route depends on specific clinical circumstances. Oral vitamin K should be used if reversal is required in 1-3 days and intravenous if reversal is required within 24 hours. Subcutaneous and intramuscular vitamin K is rarely utilized in clinical practice.
Please refer to specific guidelines for warfarin reversal.

Prothrombin Complex Concentrates: Refer to the National Advisory Committee (NAC) guidelines for specific dosing.

3. Each institution should establish processes for the management of transfusion requests that fall outside evidence-based guidelines. Each Transfusion Committee will need to decide how these orders will be managed. The boxes indicating "contact ordering physician" are meant as a guide only and can be customized with site specific instructions. The process will also vary depending upon whether the algorithm is being used prospectively or retrospectively.

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