Nova Scotia Provincial Blood Coordinating Program

Guideline for Prothrombin Complex Concentrate Utilization in Nova Scotia

Version 3.0
April 2016

PROMOTING EXCELLENCE IN TRANSFUSION MEDICINE
http://novascotia.ca/dhw/nspbcp

NOVA SCOTIA

Developed by the Prothrombin Complex Concentrate Working Group (2016)

Principal Compiler: Susan Cairns BN RN
Utilization Transfusion Practice Coordinator
Nova Scotia Provincial Blood Coordinating Program
1673 Bedford Row
Room 2123
Halifax, Nova Scotia B3J 1T1
Phone: (902) 487-0508
susan.cairns@nshealth.ca

Recommended Citation:

Nova Scotia Provincial Blood Coordinating Program (2016) *Guideline for Prothrombin Complex Concentrate Utilization in Nova Scotia* Version 3.0 Halifax, NS

Table of Contents

1 Background 4

2 Introduction 4
Table 1: Product Composition 5

3 Guideline Development and Implementation Process 5
3.1 Definitions 5
3.2 Development 5
3.3 Impact assessment 6
3.4 Endorsement 6
3.5 Implementation 6
3.6 Dissemination 6
3.7 Monitoring, reporting and evaluation 6
3.8 Review and revisions 6

4 Guideline 6
4.1 Indications for Use 6
Table 2: CHEST Guidelines for the Management of Elevated INRs while on Vitamin K Antagonist (Warfarin) therapy 7
4.2 Recommended Dosing 7
Table 3: PCC Dosing for Adults: 7
Monitoring Requirement 8
4.3 Contraindications 8

5 References 9

Appendix A – Prothrombin Complex Concentrates Working Group Members 10
Appendix B – Data Collection Tool 11

1 Background

The Nova Scotia Provincial Blood Coordinating Program (NSPBCP) provides leadership in collaborating with health care providers across the province and Canadian Blood Services (CBS) to maximize the safe and appropriate management of blood and blood products for patients in Nova Scotia. The NSPBCP maintains a surveillance program for adverse events related to transfusion therapy while ensuring appropriate standards for blood-transfusion therapy are being implemented and maintained within Nova Scotia health-care facilities.

Oral vitamin K antagonists, such as Coumadin®, are in widespread use for the prevention and treatment of thromboembolic disorders. "The major adverse effect of warfarin is bleeding. On average, the annual rate of major bleeding is 1-2% in patients on chronic warfarin, while minor bleeding events occur in 10-20% of warfarin users per year." (Thrombosis Canada 2015) Rapid reversal of anticoagulation in bleeding patients or prior to urgent surgery or other interventional treatment is critical in mitigating morbidity and mortality. When indicated, the administration of PCCs with Phytonadione (Vitamin K_1) supplementation is the most effective method for rapid reversal of anticoagulation therapy.

Prothrombin complex concentrates (PCCs) (octaplex® and Beriplex®P/N), derived from human plasma and having undergone solvent/detergent treatment and/or nanofiltration for viral, bacterial and parasite inactivation/removal, have been licensed for use in Canada by Health Canada.

2 Introduction

The objective of the *Guideline for Prothrombin Complex Concentration Utilization in Nova Scotia* is to provide clinical guidance to healthcare professionals with patient conditions who may benefit from the rapid reversal of vitamin K antagonists while providing standardization of care on the appropriate use of PCCs. Guidelines provide evidence-based information and consensus-based recommendations for consideration when making individual decisions. Guidelines should not replace the case-by-case decisions for individual patient care which are unique to each circumstance.

PCCs are indicated for patients who require rapid correction of prothrombin complex coagulation factors, i.e. the patient is taking oral vitamin K antagonists (anticoagulants) and is bleeding or requiring urgent surgery/invasive procedure. It requires, however, careful risk benefit evaluation with awareness of contraindications and laboratory follow-up for dose adjustment[1].

In Canada, the PCCs contain 4 coagulation factors (Factors II, VII, IX, X).

Table 1: Product Composition[1, 2]

One 20 mL (500 IU) vial of PCC (reconstituted) contains the following:

Factor	octaplex®[1]	Beriplex® P/N[2]
Human Coagulation Factor II	280-760 IU	380-800 IU
Human Coagulation Factor VII	180-480 IU	200-500 IU
Human Coagulation Factor IX	500 IU	400-620 IU
Human Coagulation Factor X	360-600 IU	500-1020 IU
Antithrombin III		4-30 IU
Protein C	140-620 IU	420-820 IU
Protein S	140-640 IU	240-680 IU
Heparin	80-310 IU	8-40 IU
Sodium citrate	17-27 mmol/L	~3 mmol/L

Due to the potential for thrombotic complications, treatment with PCCs should be initiated under the supervision of a clinician experienced in the treatment of coagulation disorders (i.e. emergency clinicians, hematologists, anesthetists). This caveat will ensure appropriate use, dosing and management of potential complications[1].

3 Guideline Development and Implementation Process

3.1 Definitions

Coagulopathy - "a condition in which the blood's ability to clot is impaired." Some clinicians will also refer to coagulopathy in terms of thrombotic states. "…because of the complexity of the hemostatic pathways, the two conditions can exist simultaneously." [7]

INR (International Normalized Ratio) – a standardized way to report prothrombin time (PT) normalized for the different types of PT reagents available in laboratories

Vitamin K Antagonist (VKA) - an anticoagulant inhibiting the synthesis of vitamin K dependent clotting factors (Factors II, VII, IX and X, and the anticoagulant proteins C and S). The vitamin K antagonists referred to in this guideline are oral medications.

Prothrombin Complex Concentrate (PCC) – a lyophilized plasma protein product (PPP) derived from human plasma containing the vitamin K dependent coagulation factors.

3.2 Development

In 2009, the NSPBCP convened a physician working group for the development of the *Utilization Guidelines for Prothrombin Complex Concentrates (octaplex®).* At the same time, the NSPBCP began collecting utilization data for PCCs within Nova Scotia. These guidelines were revised in 2012 and 2013 when the National Advisory Committee on Blood and Blood Products (NAC) provided updated versions of their recommendations. In 2014, NAC revised their *Recommendations for Use of Prothrombin Complex Concentrates in Canada*. The PCC WG (Appendix A) was reconvened in 2015 and the following guideline has been adapted from the 2014 NAC recommendations with the dosing recommendations based on data results from PCC utilization in Nova Scotia.

3.3 Impact assessment

The following guideline has not changed the appropriate dosing recommendations in Nova Scotia therefore this guideline would not impact appropriate current practice.

3.4 Endorsement

The Prothrombin Complex Concentrate Working Group has served as the advisory body to the NSPBCP for the development of these guidelines.

3.5 Implementation

The *Guideline for the Utilization of Prothrombin Complex Concentrates in Nova Scotia* is intended for provincial implementation.

3.6 Dissemination

The *Guideline for the Utilization of Prothrombin Complex Concentrates in Nova Scotia* guidelines will be disseminated to the NSHA and IWK for implementation.

3.7 Monitoring, reporting and evaluation

In order to monitor adherence to the *Guideline for the Utilization of Prothrombin Complex Concentrates in Nova Scotia*, PCC utilization is reported to the NSPBCP on a quarterly basis using the data collection tool in Appendix B. Annual and quarterly utilization is reported to the NSHA and IWK and strategies to optimize appropriate use are implemented in collaboration with the NSPBCP.

3.8 Review and revisions

The following guideline will be reviewed and revised as per NSPBCP policy or as new evidence and/or national guidelines become available.

4 Guideline

4.1 Indications for Use[4]

PCCs are recommended in the following situations:

1. Rapid reversal of warfarin therapy, i.e. Coumadin®/Sintrom® **or** vitamin K deficiency in patients exhibiting major bleeding manifestations.
2. Rapid reversal of warfarin therapy, i.e. Coumadin® /Sintrom® **or** vitamin K deficiency in patients requiring urgent surgical (less than 6 hours) or other interventional procedures.

NOTE – the 6 hour recommendation reflects the half life of the product and does not apply to the urgency of the surgery/procedure.[4]

PCCs should only be administered to patients with an INR (International Normalized Ratio) greater than or equal to 1.7. It is recommended the INR be available prior to administering PCCs, however, in emergent situations (i.e. major bleeding or intracranial hemorrhage) where the INR result is delayed or not available and it is known the patient is taking a vitamin K antagonist, the administration of PCCs is acceptable with the understanding the INR will be collected prior to PCC administration.

For management of vitamin K antagonist treatment with an elevated INR in the absence of bleeding, it is recommended clinicians refer to the American College of Chest Physicians (ACCP) 2012 recommendations.[3] In most of these instances, reduction of the dose of the vitamin K antagonist and/or administration of Phytonadione (Vitamin K_1) is usually sufficient for patient management.[3]

Table 2: CHEST Guidelines for the Management of Elevated INRs while on Vitamin K Antagonist (Warfarin) therapy[3]

Condition	Recommendation
INR 4.5 to 10 No evidence of bleeding	Do not administer vitamin K. Hold or lower the dose of VKA
INR greater than 10 No evidence of bleeding	Administer oral vitamin K. Hold or lower the dose of VKA
Major bleeding	Rapid reversal of anticoagulation with PCC and slow administration of vitamin K 5-10 mg IV. Do not administer plasma.

"It is critical to recognize that the use of prothrombin complex concentrates may unmask thrombotic risk factors that were being managed through the use of Vitamin K antagonists."[4]

4.2 Recommended Dosing[1]

The following dosing recommendations are based on utilization data results received from Nova Scotia hospitals since the implementation of the previous guideline (Version 2.3) - April 2013 to March 2015.

Table 3: PCC Dosing for Adults

	INR 1.7 – 5.0	INR ≥ 5.1 OR Major bleeding with an unknown INR OR Intracranial Hemorrhage
Dose of PCC	40 mL (1000 IU)	80 mL* (2000 IU)

*The recommended PCC dose of 80 mL (1000 IU) may be administered

- to patients who are on a vitamin K antagonist with an INR greater than or equal to 5.1 and the patient is bleeding, or requiring urgent surgery or invasive procedure within 6 hours
- to patients who are taking vitamin K antagonist but the INR is not known and the patient has a major bleed
- to patients who are taking a vitamin K antagonist and have an intracranial hemorrhage

For pediatric patients, consultation with a pediatric hematologist is recommended.

NOTE: The above dosing may be less than the manufacturer's recommendations contained in the product monograph. The product monograph "recommendations aim to correct factor levels to normal despite the fact normal hemostasis does not require 100% factor levels."[4]

Phytonadione (Vitamin K_1) 10 mg administered intravenously is strongly recommended.[3, 4] Intramuscular and subcutaneous administration of Phytonadione (Vitamin K_1) is not recommended.[4]

Monitoring Requirement[1]

Pre-dose monitoring: The pre-dose INR is required. There may be situations where the clinician cannot wait for the INR result prior to administering the PCC dose however the pre-PCC INR should be drawn and calculated.

Post-dose monitoring: Efficacy of dosing must be determined by testing the INR 10 - 30 minutes post PCC administration.[4]

The post-PCC administration target INR is 1.7 ***however for intracranial hemorrhage, the target INR is less than 1.3***.[5] If the target INR is not obtained after initial or subsequent doses or if there is insufficient time to wait for the vitamin K to take effect and the patient continues to bleed or to require urgent surgery or invasive procedure, consider administering an additional PCC dose of 20 mL (500 IU Factor IX activity).

It is recommended clinical outcomes (including thrombotic events) be assessed at 24 hours and upon hospital discharge or 30 days post PCC administration, whichever comes first.

4.3 Contraindications

PCCs are not indicated for the following: [4]

i. in patients with a history of heparin induced thrombocytopenia (HIT)
ii. those who have shown hypersensitivity to any ingredient in the product
iii. for the treatment of intracranial hemorrhage or other bleeding occurring as a complication of thrombolytic therapy.

PCCs are generally not recommended* for: [4]

i. elective reversal of oral anticoagulant therapy pre – invasive procedure
ii. treatment of elevated INRs without bleeding or need for surgery or other interventional treatment (refer to the ACCP 2012 recommendations)
iii. massive transfusion
iv. coagulopathy associated with liver dysfunction
v. disseminated intravascular coagulopathy (DIC)
vi. utmost caution should be used in patients with a recent (within three months) history of thrombosis (myocardial infarction, ischemic stroke or thromboembolism)

Special patient populations*:[4]

i. There is insufficient published evidence to recommend for use of PCCs in pediatric patients, pregnant and lactating women. Caution should be exercised if used in pregnancy, particularly in the peripartum/early postpartum period because of the heightened tendency for thrombosis.
ii. The use and dosing of the product for congenital factor II or X deficient patients should be at the discretion of the bleeding disorder/hemophilia clinic.
iii. There is insufficient published evidence to recommend PCCs for the reversal of direct thrombin inhibitors[4] (i.e. Argatroban, Bivalirudin, Dabigatran) or factor Xa inhibitors (i.e. Apixaban, Dalteparin, Danaparoid, Enoxaparin, Tinzaparin, Fondaparinux, Rivaroxaban). There is published evidence suggesting PCCs may be effective in the reversal of direct anti-Xa (Rivaroxaban) therapy *in animal studies* and in healthy volunteers however no consensus on the appropriateness and dosing has been determined.[4]

**There may be extenuating clinical circumstances necessitating the use of PCCs in these clinical situations where the benefit outweighs the risk. They should be evaluated on a case-by-case basis with a clinician experienced in the use of this product. If the decision is made to use the product off-label in liver dysfunction and DIC, consult the product monograph for further recommendations (e.g. the need for antithrombin levels or replacement).*[4]

5 References

1. Octapharma Canada, Inc. (2014) Octaplex® Product Monograph. Brampton, Ontario.

2. CSL Behring Canada, Inc. (2015) Beriplex®P/N Product Monograph. Ottawa, Ontario

3. Holbrook, A. et al (2012) Evidence-Based Management of Anticoagulant Therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines *Chest.* 2012 Feb;141(2 Suppl):e152S-84S. doi: 10.1378/chest.11-2295.

4. National Advisory Committee on Blood and Blood Products. (2014). Recommendations for Use of Prothrombin Complex Concentrates in Canada.

5. Kuramatsu, J.B. et al. (2015) Anticoagulant Reversal, Blood Pressure Levels, and Anticoagulant Resumption in Patients with Anticoagulant-Related Intracranial Hemorrhage *JAMA.* 2015; 313(8):824-836. Doi:10.1001/jama.2015.0846

6. NSPBCP (2013) *Guideline for the Prothrombin Complex Concentrates in Nova Scotia* Version 2.3 Halifax, NS

7. Hunt, B.J. (2014) Bleeding and Coagulopathies in Critical Care *N Engl J Med* 2014; 370:847-859 DOI: 10.1056/NEJMra1208626

Appendix A – Prothrombin Complex Concentrates Working Group Members

The NSPBCP acknowledges the tremendous and diligent work of the provincial PCC WG for providing valuable expertise and contributions in the development of this guideline.

Prothrombin Complex Concentrates Working Group	
Dr. Frank Cragg	Medical Leader (Blood Transfusion and Hematology), Cape Breton Regional Hospital
Dr. Brian Jollymore	Medical Director, Blood Transfusion Services, Valley Regional Hospital
Dr. Eiad Kahwash	Medical Director, Canadian Blood Services, Nova Scotia and Prince Edward Island
Dr. Blaine Kent	Chief, Division of Cardiac Anesthesia; Surgical Director of Perioperative Blood Management Program, Queen Elizabeth II Health Sciences Centre
Dr. Jean F. Legare	Cardiac Surgeon, Queen Elizabeth II Health Sciences Centre
Dr. Stephen Phillips	Stroke Neurologist, Queen Elizabeth II Health Sciences Centre
Dr. Victoria Price	Pediatrician/Hematologist, IWK Health Centre
Dr. Irene Sadek	Medical Director, Pathology & Laboratory Medicine, Department of Pathology and Laboratory Medicine, Queen Elizabeth II Health Sciences Centre
Nova Scotia Provincial Blood Coordinating Program (NSPBCP)	
Dr. Sudeep Shivakumar	Clinical Advisor
Marina Hamilton	Program Manager
Susan Cairns	Utilization Transfusion Practice Coordinator

Appendix B – Data Collection Tool

Massive Bleeding Data Collection Form

(Blood Components & Products/PCC/rFVIIa)

Province ID# _____ Hospital ID# _____ Date | Y | Y | Y | Y / M | M / D | D |

Patient HCN _____ Patient First & Last Name _____

Birth date | Y | Y | Y | Y / M | M / D | D | Gender: [ ] Male [ ] Female Weight _____(kg)

Ordering Physician CPSNS # _____ Physician Name _____ Specialty _____

Location (circle): Emerg / ICU / OR / Floor / Clinic / Other *(specify)* _____

Massive Bleeding/Transfusion

Massive Bleeding [ ] No [ ] Yes – *specify*
[ ] Trauma [ ] Surgical [ ] Obstetrical [ ] Medical [ ] Other *Specify* _____
On Anticoagulants - [ ] No [ ] Yes – *specify* _____

MTP Activated [ ] No [ ] Yes **Time activated:** _____ (hhmm)
MTP Activated by: [ ] Lab [ ] Physician – *specify blood components issued at activation*: [ ] None
[ ] Yes – RBC _____ units Plasma _____ mL Platelets _____ units Other _____

Tranexamic Acid [ ] No [ ] Yes Time administered _____ (hhmm)

Total Blood Products/Components transfused *(include above components)* [ ] None [ ] Yes - s*pecify*

RBC _____ units
Plasma _____ mLs
Platelets _____ doses
Cryo _____ units

Other: (Fibrinogen, ATIII, DDAVP …) include volume/dose given
1. _____
2. _____
3. _____

platelet doses requested from CBS *(for facilities where platelets are not inventoried)* _____ doses

-

PCC

PCC administered [ ] No [ ] Yes Product administered (*circle*) – octaplex® / Beriplex®P/N
Congenital Factor II or X Deficiency [ ] No [ ] Yes (specify) _____
Vitamin K Deficiency [ ] No [ ] Yes
Patient on oral anticoagulants [ ] No [ ] Coumadin® [ ] Sintrom® [ ] Other _____

- Actively Bleeding [ ] No [ ] Yes *Specify* _____
- Requiring urgent surgical or invasive procedure [ ] No [ ] Yes
  Date of Procedure _____(YYYY/MM/DD) *Specify procedure* _____

Initial INR result _____ INR result known prior to issuing PCC [ ] Yes [ ] No

Phytonadione (Vitamin K®) administered [ ] No [ ] Yes Dose_____ mg.

Initial PCC dose_____ mL	**Time** _____ (hhmm)	**Post INR**_____	**Time** _____ (hhmm)
PCC Dose 2_____ mL	Time _____ (hhmm)	Post INR _____	Time _____ (hhmm)
PCC Dose 3_____ mL	Time _____ (hhmm)	Post INR _____	Time _____ (hhmm)
PCC Dose 4_____ mL	Time _____ (hhmm)	Post INR _____	Time _____ (hhmm)

rFVIIa

If reporting rFVIIa use, complete the *Massive Bleeding/Transfusion* section.
rFVIIa administered [ ] No [ ] Yes Total rFVIIa dose administered _____ mg
Reason for administration _____

Clinical Disposition

Bleeding stopped [ ] No [ ] Yes [ ] Unknown or N/A Patient discharged [ ] No [ ] Yes
Patient survived [ ] No [ ] Yes Date of death | Y | Y | Y | Y / M | M / D | D |
Did the patient develop arterial/venous thromboembolism during hospitalization? [ ] No [ ] Yes [ ] Unknown or N/A
Comments / Additional Information

Signature _____ Fax to NSPBCP 902-422-0893

NSPBCP Use Only	Date:_____ Initials: _____	PCC	rFVIIa	Massive Bleeding/Transfusion
		[ ] L	[ ] UL-I	[ ] Guide followed
		[ ] UL-I	[ ] UL-N	[ ] Guide not followed
		[ ] UL-N	Entered into Database – Date:	Initials: