NAC Position Statement on Patient Blood Management

NAC POSITION STATEMENT ON PATIENT BLOOD MANAGEMENT

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LIST OF ABBREVIATIONS

ESA	Erythropoietin stimulating agent
GI	Gastrointestinal
IT	Information Technology
IV Iron	Intravenous iron
NSAIDS	Non- steroidal anti-inflammatories
ONTraC	Ontario Nurse Transfusion Coordinator
PBM	Patient Blood Management
TACO	Transfusion Associated Circulatory Overload
TRALI	Transfusion Associated Lung Injury

SECTION 1.0: PREAMBLE

Patient Blood Management (PBM) is the timely application of evidence-based medical and surgical concepts designed to maintain hemoglobin concentration, optimize hemostasis and minimize blood loss in an effort to improve patient outcome.[1] Framework for PBM programs may vary whether in a surgical setting (pre-operative, intra-operative, and post-operative)[2] or by goal (stop/minimize blood loss and diagnostic phlebotomy, diagnose and treat coagulopathy, manage anemia, and improve tolerance of anemia)[3]. The aim, regardless of framework, is to improve patient outcomes and make patients the center of care.

PBM programs consistently demonstrate reduced transfusion utilization and cost avoidance[4]; and they frequently demonstrate reduced hospital length of stay, reduced morbidity, reduced mortality, and overall improved patient outcomes[5]. These benefits are in contrast to the increased recognition that ignoring anemia or utilizing transfusion to treat anemia may increase complications including: infection[6], thrombosis[7], stroke/myocardial infarction[8], transfusion related immunomodulation (which may increase cancer progression and/or recurrence)[9],[10], and transfusion reactions such as transfusion associated circulatory overload (TACO) and transfusion associated lung injury (TRALI)[11].

In many institutions, patient blood management is the standard of care[12]. The World Health Organization issued a resolution in 2010 to improve patient safety by implementing patient blood management programs,[13] and in 2021 issued an updated policy brief calling for an urgent need to implement patient blood management[14]. Specifically, they state, "All Member States should act quickly through their ministry or department of health to adopt their national PBM policy, install the necessary governance, and reallocate resources to improve the population health status and individual patient outcomes while reducing overall health care expenditures." World-wide, there has been country-wide implementation in Austria, the Netherlands[15], and Western Australia[16]. While there are some references to PBM by Canadian Blood Services[17], and principles may be found in the NAC blood shortages document[18], more widespread application across the healthcare spectrum is necessary to improve health care provision and blood utilization in Canada. Many processes need to be aligned, and it is short sighted to attempt to perfect anemia management once a blood shortage occurs. PBM is interdisciplinary and goes beyond transfusion; cooperation and education amongst nursing, physicians, administration, pharmacy, laboratory, and perfusion staff is necessary. PBM should also reflect the patient's medical history, preferences and values.

SECTION 2.0: COMPONENTS OF A PBM PROGRAM

Successful Patient Blood Management Programs include the following[19]:

Education - Many medical practitioners are accustomed to certain practice behaviors that become outdated over time[20]. An example is the transfusion of two units of red blood cells in response to anemia. This has become a focus for Choosing Wisely's, "Why Use Two When One Will Do" campaign[21]. Likewise, transfusion thresholds have steadily decreased over time in response to higher quality evidence advocating for more restrictive thresholds. Unfortunately, implementation of this evidence has been slow and heterogeneous. Finally, while the evidence has supported the use of intravenous iron (IV iron) and erythropoietin stimulating agents (ESA) to reduce transfusion needs[22], their implementation into practice lags. The reasons for this delay are many, but lack of medical practitioner education on these transfusion alternatives represents a significant barrier to their adoption.

Physician resources - Many programs have a physician director for managing referrals and intervention of complex forms of anemia. A lack of physician education and assigned responsibility for managing anemia results in patients missing opportunities for optimization and better outcomes prior to and during their hospital admission.

Nursing resources - Nursing care forms the backbone of patient blood management programs in terms of direct patient care. A dedicated nursing position ensures continuity of care. Currently in Canada, the Ontario Nurse Transfusion Coordinator (ONTraC) program exemplifies the important role of nursing in patient blood management[23]. Not all sites in Ontario have this program, and most sites outside of Ontario have no formal program. The ONTraC program has one of the best toolkits available for hospital implementation[24].

Administrative resources - Scheduling patient consultations, interventions, and follow-up is also necessary to maintain patient flow in their care journey. Developing and employing data tracking to ensure quality metrics are achieved is also important.

Physical resources - Some aspects of patient blood management include administration of intravenous and subcutaneous injections, which require patient assessment and monitoring. The best example is intravenous iron. Depending on the IV iron formulation chosen, total chair time to restore iron stores may be as short as 1 hour or up to 10 hours[25]. This requires monitored space to accommodate patients undergoing treatment, as well as nursing and physician resources to staff and supervise administration.

Timing to critical events - A robust system identifies patients well in advance of their surgical or obstetrical delivery date. To utilize low-cost oral iron requires nearly three months on average to restore iron in deficient patients. Most surgical systems do not notify patients or practitioners of upcoming dates with enough time to utilize oral supplements. Peak effect for IV iron and ESA still requires several weeks of planning to optimize anemia and limit transfusion, although there is some evidence that even a single day results in some improvement[26].

Pharmacy resources - Pharmacy needs to be actively engaged as most budgets are isolated from one another. Labile blood components are funded by a transfusion budget, but adjunctive therapy including IV iron and ESA are funded by a pharmacy budget through exceptional drug status, private insurance, or a patients' own funds. The savings are a result of reduced transfusion costs, activity costs (compatibility

testing, inventory management), and reduced hospital costs when the hospital stay is reduced. Conversely, treating anemia without transfusion often increases the pharmaceutical cost. As a net equation, PBM reduces overall system costs. Therefore, pharmacists need to be actively engaged in ensuring appropriate resource management and reimbursement, and to consider the risks and benefits of labile blood components as compared to the risks and benefits of a medication.

Medication funding - Medications specifically shown to reduce transfusion or treat anemia should be considered. Specifically, antifibrinolytics (tranexamic acid)[27], IV iron (ferric gluconate, iron sucrose, ferric derisomaltose)[28], and ESAs (Darbopoetin, Epoetin alpha)[29] have a significant transfusion-sparing effect and should be publicly funded.

Laboratory Resources - Laboratory clinicians can often improve diagnostic accuracy and timeliness to assess patient response to therapy. An example would be measuring reticulocyte markers (early red blood cell production) in response to oral iron to assess the need to progress to IV iron or add an ESA. Many laboratories also oversee point of care testing which may reduce the volume of blood lost by patients during diagnosis. Similarly, laboratories can strive to reduce unnecessary diagnostic phlebotomy, duplicate or mislabeled specimens by use of positive patient identification, and use of smaller tubes or those with less vacuum to collect blood samples.

IT support - Data drives decisions and informs future management. A robust system to capture pre and post implementation allows evaluation of value-added patient blood management and helps drive future clinical decisions. Implementing clinical decision support for physician order entry has been shown to reduce unnecessary transfusions[30].

Perfusion resources - Not every hospital will have perfusion personnel, but where present and in appropriate situations, perfusionists provide cell saver support in massive hemorrhage and high-risk operations. They are an integral part of providing safe cardiovascular surgical care and introducing measures to reduce the risk of transfusion in cardiac surgery.

SECTION 3.0: RECOMMENDATIONS

A. Systemic Recommendations

1. All hospitals should work with their provincial Ministry of Health and health sector partners to implement PBM as a best practice that improves patient outcomes and system efficacy. A multimodal perioperative PBM program should be instituted in all surgical programs to address preoperative, intra-operative, and postoperative anemia. The resources outlined in Section 2, which are required for successful implementation of patient blood management, should be provided on a site-by-site basis with consideration of clinical need and system resources.

2. Provinces should encourage hospitals to participate in initiatives including Choosing Wisely and Using Blood Wisely which align with patient blood management principles. Providing order sets, and screening for single unit transfusions and restrictive transfusion thresholds (less than 70g/L in all patients except those at risk of ischemia where the threshold is less than 80g/L) reduces blood utilization without adding cost.

3. Educational resources should foster the development of local patient blood management leaders and champions. All health care practitioners should be aware that anemia (hemoglobin less than 130g/L in peri-operative patients) increases morbidity and mortality. This is true of pre-existing anemia and hospital acquired anemia. Hospitals should recognize that routine or avoidable diagnostic blood draws can result in hospital acquired anemia and prolong patient recovery. Stopping and minimizing blood loss requires interdisciplinary efforts and should be a primary pillar for PBM programs.

B. Clinical Recommendations

4. All patients undergoing surgery or delivery should be screened for anemia at least 6 weeks prior to their anticipated surgical or delivery date.

5. Appropriate referral to a specialist for investigation and management of underlying conditions is recommended and may include gastroenterology, gynecology, hematology, nephrology, or others according to the underlying etiology.

6. In anemic patients with ferritin less than 30ucg/L and more than six weeks to an operative or delivery date, oral iron therapy should be instituted.

7. In anemic patients with ferritin less than 30 ucg/L and less than six weeks to an operative or delivery date, IV iron therapy should be instituted.

8. In patients at risk of anemia and ferritin less than 30ucg/L oral iron therapy should be instituted.

9. In patients with anemia and iron restricted erythropoiesis with ferritin greater than 30ucg/L and TSAT less than 20%, IV iron therapy should be instituted.

10. In patients with inadequate response to IV iron or when iron sequestration or inflammation limits the bioavailability of iron, an ESA should be considered on a case-by-case basis.

11. In patients with anemia and evidence of inflammation or renal failure where an ESA is indicated, it should be combined with IV iron.

12. When an ESA is used, concomitant use of thromboembolic prophylaxis should be considered on a case-by-case basis.

13. Anemia should be corrected prior to all elective surgery. Institutions should have guidelines on postponing surgery until anemia is corrected.

14. In patients who develop postoperative or post-hemorrhage related anemia, IV iron is recommended[31].

15. The risk of surgical bleeding, urgency of surgery, and type of anticoagulation should be addressed to reduce blood loss. For specific recommendations for individual agents, resources such as Thrombosis Canada or a local perioperative thrombosis expert should be consulted.

16. During hemorrhage, permissive hypotension or deliberately induced hypotension should be considered while balancing the risk of blood loss and preservation of vital organ perfusion.

17. When substantial blood loss is anticipated, acute normovolemic hemodilution should be considered.[33,34,35]

18. When substantial blood loss is anticipated or encountered, intraoperative cell salvage should be considered.

19. When substantial blood loss is anticipated or encountered, or the patient is involved in trauma or post-partum hemorrhage, antifibrinolytics (tranexamic acid) should be administered.

20. When patients are recovering from anemia, other physiologic parameters should be addressed to reduce oxygen requirements. Hypothermia should be avoided with active warming. Processes that contribute to hospital acquired infections should be minimized, including nasogastric tubes and foley catheters.

Patients must be placed at the center of care. Improving long term outcomes and reducing morbidity and mortality is necessary to improve the quality of care delivered to Canadians. Implementing multidisciplinary strategies as part of a patient blood management program has the potential to improve outcomes and simultaneously reduce system costs. In the interest of improving care to its citizens, every province should develop a patient blood management program (*Figure 1)*.

Current clinical recommendations already exist and examples are offered from ONTraC[24], the American Society of Hematology,[32] and the Mayo Clinic[2.] For visualization purposes, the algorithm from ONTraC is attached.

A cost comparison using a single unit of blood as a cost comparison in managing anemia is attached (*Table 1*). While transfusion of a single unit of blood may raise hemoglobin levels temporarily, the transfused cells are generally destroyed more rapidly than endogenous cells and contribute to inhibiting production of endogenous cells. Transfused blood is not equivalent to endogenous production of blood.

SECTION 4.0: ALGORITHMS

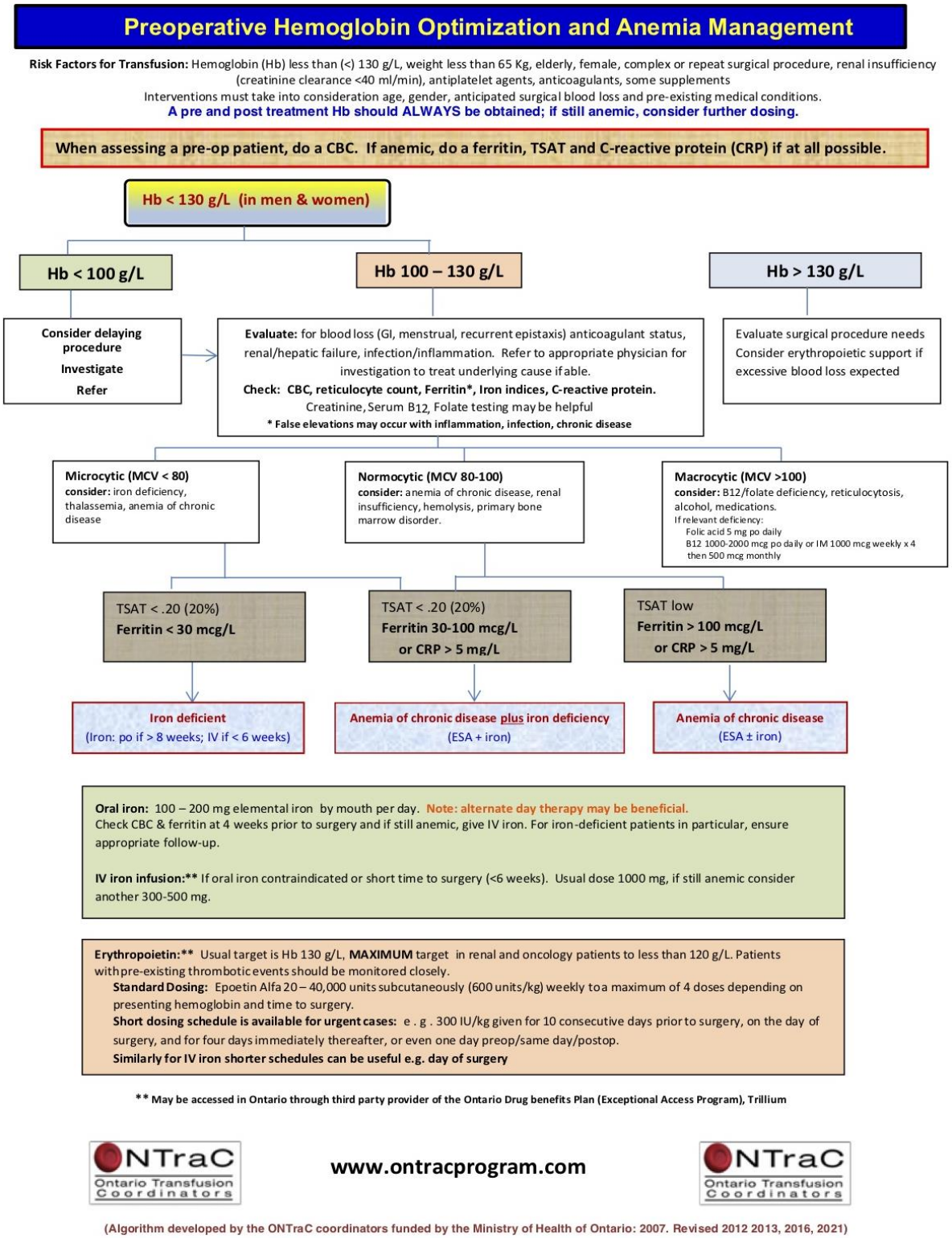

Figure 1 *Preoperative Hemoglobin Optimization and Anemia Management*

SECTION 5.0 COST COMPARISON OF ANEMIA STRATEGIES

Intervention	Dose	Cost	Duration of therapy	Peak effect	Total acquisition cost	Additional costs - nursing, lab, testing, chair time (may vary)	Change in hemoglobin (g/L)	Cost/g/L increase	Relative Cost per g/L increase in hemoglobin compared to 1 unit RBC	Cost comparator to 1 unit RBC (acquisition + additional costs)
red blood cells	1 unit	$446.00	120min x 1	end of infusion; shorter 1/2 life than endogenous cells	$446.00	$328.30	10	$77.43	1.00	1.00
oral iron salts	100mg elemental daily	$0.28	13-26 weeks	13-26 weeks	$39.20	$28.47	28	$2.42	0.03	0.09
iron sucrose	300mg	$112.50	90min x 4	5-8 weeks	$450.00	$623.15	39	$27.52	0.36	1.39
iron isomaltoside	1200mg	$540.00	60 min x 1	5-8 weeks	$540.00	$64.72	39	$15.51	0.20	0.78
Epoetin alfa (healthy)	40,000 units q weekly	$486.79	1 min x 4 weeks	4-6 weeks	$1947.16	$76.84	31	$65.29	0.84	2.61
Epoetin alfa (pre-op orthopedics)	40,000 units (600U/kg for 70kg) q weekly	$486.79	1 min x 4 weeks	4-6 weeks	$1947.16	$76.84	14.4	$140.56	1.82	2.61
Epoetin alfa (pre-op orthopedics)	20,000 units (300U/kg for 70kg q daily x 14 days	$285.00	1 min x 14 days	4-6 weeks	$3990.00	$268.94	7.3	$583.42	7.53	5.50
	Note 1: A change in hemoglobin does not imply equal efficacy. 1 unit of transfused blood temporarily improves hemoglobin levels, but suppresses endogenous erythropoeisis, and cells are broken down more rapidly than endogenous cells. Conversely endogenous red blood cells produced with appropriate supplementation are expected to have a normal lifespan. The above table does not take into account increased hospital time, morbidity, and mortality associated with red blood cell transfusion.									
	Note 2: Comparison of erythropoietin dosing on an accelerated daily schedule near the time of operation vs weekly schedule for one month pre-operatively underscores the need for system design to allow early intervention. Anemia management is more cost effective with 6 week preoperative planning. However, even a single dose of erythropoietin may be adequate to prevent transfusion. Spahn DR, et al. Effect of ultra-short-term treatment of patients with iron deficiency or anaemia undergoing cardiac surgery: a prospective randomised trial. *Lancet*. 2019;393(10187):2201-2212									
	Sources:									
	1 unit RBC raises hemoglobin 10g/L - https://professionaleducation.blood.ca/en/transfusion/clinical-guide/blood-components									
	Cost of 1 unit RBC courtesy of Canadian Blood Services									
	Additional Costs of RBC administration in Canada $243.10 - Lagerquist, O., Poseluzny, D., Werstiuk, G., Slomp, J., Maier, M., Nahirniak, S. and Clarke, G. (2017), The cost of transfusing a unit of red blood cells: a costing model for Canadian hospital use. VOXS, 12: 375-380. These costs may be higher ($522.78 cost adjusted CAD) - Amin M, Fergusson D, Wilson K, et al. The societal unit cost of allogenic red blood cells and red blood cell transfusion in Canada. *Transfusion*. 2004;44(10):1479-1486. The total cost of $243.10 + 120 min infusion time x $0.71/minute chair time to keep comparisons similar.									
	Cost of iron salts - performed at a local pharmacy for ferrous sulphate and ferrous fumarate - between $0.17-$0.28 per pill; taken daily for 20 weeks (14 weeks to improve hemoglobin and additional 6 for iron stores)									
	Efficacy of Iron salts - Alleyne, M., Horne, M. K., & Miller, J. L. (2008). Individualized treatment for iron-deficiency anemia in adults. *The American journal of medicine*, *121*(11), 943–948. Moe S, Grill AK, Allan GM. Newer iron supplements for anemia. *Can Fam Physician*. 2019;65(8):556.									
	Iron sucrose effect on hemoglobin after 1200mg IV iron average increase 32.9-45.8g/L (average 39g/L increase); 100mg iron is present in 200mL whole blood which equates to 30g Hb; In a 70kg adult with 70ml/kg blood volume this rise equates to a 6.1g/L increase in Hb per 100mg of iron administered, but the effects are not linear - Cançado RD, de Figueiredo PO, Olivato MC, Chiattone CS. Efficacy and safety of intravenous iron sucrose in treating adults with iron deficiency anemia. *Rev Bras Hematol Hemoter*. 2011;33(6):439-443. doi:10.5581/1516-8484.20110119									
	Cost of iron sucrose and isomaltoside - CADTH Pharmacoeconomic Review - https://www.cadth.ca/iron-iii-isomaltoside-1000 - $37.50/100mg iron sucrose; $45.00/100mg iron isomaltoside;									
	Additional Costs of iron administration taken from the CADTH Pharmacoeconomic review: $37/hr nursing time - with allowances as per Pettigrew review infusion device $7.94, chair time $0.71/minute, 150 minutes for sucrose, 60 minutes for isomaltoside, labwork - 1 time each $28.47, 4 visits for iron sucrose (300mg x 4 visits), 1 visit for iron isomaltoside (1200mg single infusion)									
	Cost of Epoetin alfa from Saskatchewan Formulary $14.25/1000 units up to 20,000 units, and $12.17/1000 units for 40,000 units available at: https://formulary.drugplan.ehealthsask.ca/SearchFormulary/BG/706942									
	Additional costs of Epoetin alfa - 0.5 hour nursing time per dose administered x $37/hr and 1 minute chair time at $0.71/minute									
	Change in hemoglobin in Normal volunteers with epoetin alfa was 31 g/L with either dosing schedule of 150U/kg 3x/week or 40,000 units/week - Eprex product monograph - https://pdf.hres.ca/dpd_pm/00041771.PDF									
	Change in hemoglobin in pre-operative orthopedics was 14.4g/L on average using 600U/kg/week and 7.3g/L on average using 300U/kg for 10 days preoperatively, and 4 days postoperatively (Eprex product monograph: https://pdf.hres.ca/dpd_pm/00041771.PDF)									

Table 1 *Cost Comparison of Anemia Strategies*

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