POSITION STATEMENT ON PATIENT BLOOD MANAGEMENT

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TABLE OF CONTENTS

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ABBREVIATIONS

ESA	Erythropoietin Stimulating Agent
Hb	Hemoglobin
IV Iron	Intravenous Iron
NAC	National Advisory Committee on Blood and Blood Products
ONTraC	Ontario Nurse Transfusion Coordinator
PBM	Patent Blood Management
RBC	Red Blood Cell

DEFINITIONS

Patient Blood Management – a patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving a patient’s own blood, while promoting patient safety and empowerment.

SUMMARY OF REVISIONS

June 2026

General	Formatting updated throughout. Abbreviations updated, definitions, acknowledgments and summary of revisions sections added. References updated and added throughout.
Section 1.0	Patient blood management definition updated.
Section 2.0	Updates made to education, administrative resources, medication funding, and laboratory resources subsections.
Section 3.0	New recommendations added: m-q and z. Substantial revisions made to recommendations: b-d, f-i, t, and v. Previous section 4.0 'Algorithms' was merged to be included in section 3.0.
Section 4.0	Table 1: Cost comparisons of anemia strategies updated. Table 2: Inflation cost of epoetin alfa added.
Appendix A	Appendix A: Table 1 & 2 Notes and Assumptions added to reduce visual clutter from tables.
Appendix B	Appendix B: Improving Iron Absorption added.
Appendix C	Appendix C: Previous Authors added.

1.0 INTRODUCTION

Patient Blood Management (PBM) is a patient-centered, systematic, evidence-based approach to improve patient outcomes by managing and preserving a patient's own blood, while promoting patient safety and empowerment.[1] Frameworks for PBM programs may vary whether in a surgical setting (pre-operative, intra-operative, and post-operative)[2] or by goal (to 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] frequently demonstrate reductions to hospital length of stay, morbidity, and mortality, and show 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 and transfusion associated lung injury.[11]

In many institutions, PBM is the standard of care.[12] The World Health Organization issued a resolution in 2010 to improve patient safety by implementing PBM programs,[13] and in 2021 issued an updated policy brief calling for an urgent need to implement PBM.[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.” In 2024, the World Health Organization published a multidisciplinary guidance document for systematic implementation of PBM.[15]

World-wide, there has been country-wide implementation in Austria, the Netherlands,[16] and Western Australia.[17] While there are some references to PBM by Canadian Blood Services,[18] and principles may be found in the National Advisory Committee on Blood and Blood Products (NAC) blood shortages document,[19] more wide-spread 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, physician, administration, pharmacy, laboratory, and perfusion staff is necessary. PBM should also reflect the patient’s medical history, preferences, and values.

2.0 COMPONENTS OF A PATIENT BLOOD MANAGEMENT PROGRAM

Successful Patient Blood Management Programs include the following:[20]

Education - Many medical practitioners are accustomed to certain practice behaviours that become out-dated over time.[21] An example of this is the transfusion of two units of red blood cells (RBCs) in response to anemia. This has become a focus for Choosing Wisely’s “Why Use Two When One Will Do” campaign.[22] Likewise, many 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. This not only affects transfusion, but also lab reference values and clinical indications for medication administration such as intravenous iron (IV iron). While the evidence has supported the use of IV iron and erythropoietin stimulating agents (ESA) to reduce transfusion needs,[23] their implementation is poor.[24] Lack of medical practitioner education, appropriate laboratory reference alerts, and pharmacy availability 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 often forms the backbone of PBM 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 PBM.[25] 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.[26]

Administrative resources - Scheduling patient consultations, interventions, and follow-up is also necessary to maintain patient flow in their care journey. A key component is coordinating the timing of surgery with the timing of patient optimization. The patient and their PBM care team should receive early notification (at least six weeks) prior to surgery to coordinate their optimization strategy.

Physical resources - Some aspects of PBM include administration of intravenous and subcutaneous injections, which require patient assessment and monitoring. The best example of this is IV iron. Depending on the IV iron formulation chosen, total chair time to restore iron stores may be as short as 15 minutes or as long as 10 hours.[27] 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.[28,29]

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 ESAs, are funded by a pharmacy budget through exceptional drug status, private insurance, or a patients' own funds. Savings in PBM 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 funded in PBM programs. Specifically, antifibrinolytics (tranexamic acid),[30] IV iron (ferric gluconate, iron sucrose, ferric derisomaltose, ferric carboxymaltose),[31] and ESAs (Darbopoetin, Epoetin alfa)[32] have a significant transfusion-sparing effect and should be publicly funded. Access to these medications is inequitable across jurisdictions in Canada, putting patients at increased risk of transfusion and associated complications (see Section 1.0). It is untenable that a patient with a treatable underlying cause of anemia such as iron deficiency should be provided with an inferior treatment such as a blood transfusion when hemodynamically stable. On a gram per litre increase in hemoglobin (Hb) basis, the use of IV iron surpasses that of a unit of RBCs by a factor of three for the same cost (see Table 1: Cost comparisons of anemia strategies). Moreover, IV iron has a superior safety profile with fewer side effects and lower morbidity and mortality compared to RBC transfusion. Whereas transfusion suppresses erythropoiesis and prolongs the duration of endogenous Hb recovery, the use of IV iron (and ESAs) supports the recovery of a patient's own RBCs.

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 RBC 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,[33,34] duplicate or mislabeled specimens by use of positive patient identification, and use of smaller tubes[35] or those with less vacuum to collect blood samples. One universal barrier to optimal PBM therapy that the laboratory can eliminate is the introduction of clinically relevant Hb and ferritin thresholds rather than population or analyzer-based thresholds. For example, females have higher transfusion rates and associated morbidity and mortality following surgery due to normalized lower Hb levels.[31,36,37] Laboratories should flag all Hb levels in adults less than 130g/L as abnormal.[38,39] Likewise ferritin thresholds are reported as diagnostically accurate with very low levels (less than 15ucg/L) but the clinical reference range for improving patient function and outcomes is at least 30ucg/L and probably 50ucg/L in most adult patients.[39-44] In children this value should be at least 20ucg/L.[43]

Information technology support - Data drives decisions and informs future management. A robust system to capture standardized pre and post implementation data allows evaluation of value-added PBM and helps drive future clinical decisions.[45] Implementing clinical decision support for physician order entry has been shown to reduce unnecessary transfusions.[46]

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.

3.0 RECOMMENDATIONS

3.1 Systematic Recommendations

a) All hospitals should work with their provincial/territorial Ministry of Health and health sector partners to implement PBM as a best practice that improves patient outcomes and system efficacy. A multimodal, peri-operative PBM program should be instituted in all surgical programs to address pre-operative, intra-operative, and post-operative anemia. The resources outlined in Section 2.0, which are required for successful implementation of PBM, should be provided on a site-by-site basis with consideration of clinical need and system resources.[15]

b) Provinces/territories should encourage hospitals to participate in initiatives including Choosing Wisely, Using Blood Wisely, and Using Labs Wisely which align with PBM principles. Providing order sets, and screening for single unit transfusions and appropriate transfusion thresholds reduces blood utilization without adding cost. Current appropriate thresholds are defined as less than 70g/L in most patients (it may be even lower in asymptomatic and chronic anemia); [47-49] less than 80g/L in those at risk of ischemia, and less than 90g/L in myocardial infarction[50] and traumatic brain injury.[51]

c) Educational resources should foster the development of local PBM leaders and champions. All health care practitioners should be aware that anemia (Hb less than 130g/L in all adults) increases morbidity and mortality. The risk to women is disproportionately higher than men at lower Hb levels, therefore Hb thresholds should not discriminate.[38,39,44] 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.[33-35] Stopping and minimizing blood loss requires interdisciplinary efforts and should be a primary pillar for PBM programs.

3.2 Clinical Recommendations

d) All patients undergoing surgery or delivery should be screened for anemia (Hb less than 130g/L in all adults) at least six weeks prior to their anticipated surgical or delivery date. When present, subsequent investigations should be directed at elucidating the mechanism (i.e. iron deficiency) and source (i.e. gastrointestinal losses). Using the mean corpuscular volume from a complete blood count is inadequate to screen for iron deficiency.[52] Ferritin is preferred in an otherwise healthy population, but serum iron or transferrin saturation is preferred in the setting of myocardial infarction,[53] congestive heart failure,[54] renal failure,[55] cancer, systemic infection, or other inflammatory conditions. Reference ranges for ferritin from most laboratories use diagnostic values below the clinically important values of 30-50ucg/L[41] and relying on flagged values of 8-15ucg/L will miss relevant cases of iron deficiency.[42]

e) 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.

f) In anemic patients (Hb less than 130g/L in all adults) with ferritin less than 30-50ucg/L and more than six weeks to an operative or delivery date, oral iron therapy should be instituted. While ferritin less than 30ucg/L is highly sensitive and specific, patients who exhibit symptoms of iron deficiency may benefit from iron replacement targeting a ferritin of 50-100ucg/L.[41]

g) In anemic patients (Hb less than 130g/L in all adults) with ferritin less than 30-50ucg/L and less than six weeks to an operative or delivery date, IV iron therapy should be instituted.

h) In patients at risk of anemia (Hb greater than 130g/L but at risk of bleeding) and ferritin less than 30-50ucg/L, oral iron therapy should be instituted.

i) In patients with anemia (Hb less than 130g/L in all adults) and iron restricted erythropoiesis, inflammation, or tissue damage, ferritin is unreliable[40,53] and serum iron and total iron binding capacity should be measured and used to guide therapy instead. For this population, IV iron therapy should be instituted for transferrin saturation less than 20% in most patients, although 24% is suggested in heart failure,[54] and 30% in kidney failure.[55]

j) 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.

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

l) When an ESA is used, concomitant use of thromboembolic prophylaxis should be considered on a case-by-case basis.[56]

m) Although iron deficiency is the most common nutritional deficiency in Canada and worldwide, other deficiencies should be considered on a case-by-case basis.

n) Folate deficiency is rare in the general population when white fortified flour is consumed,[57] but whole wheat and alternative flours are not fortified with folate.[58] When non-fortified flour is consumed, folate deficiency may be present in up to 14% of the population.[59] Serum folate testing has a low positive predictive value and testing is not routinely recommended, but oral replacement is cheap and effective in those considered at risk.[60]

o) Vitamin B_{12} deficiency affects about 5% of the younger Canadian population but is higher in vegans, vegetarians, and the elderly.[61] Testing is readily available and diagnostic when levels are less than 148pmol/L. Marginal deficiency at levels less than 221pmol/L are unlikely to result in anemia, but may be associated with complications in surgery and anesthesia.[62] Treatment can be either intramuscular or oral depending on severity and response to treatment.

p) A protein deficient diet (prolonged periods less than 0.7g/kg/day) produces anemia. This is more common in the elderly and institutionalized and should be considered in patients with frailty. Increased protein intake is recommended in the peri-operative period and patients should consider consuming between 2-2.5g/kg/day while recovering.[63]

q) Other micronutrient deficiencies such as copper may contribute to anemia,[64] but diagnostic testing can be challenging. Copper in particular appears to be important for utilization of iron and avoidance of free radical formation. Vitamins C, K, D, and thiamine deficiency are associated with poor wound healing, bleeding, delirium and neurological complications.[65]

r) Anemia should be corrected prior to all elective surgery. Institutions should have guidelines on postponing surgery until anemia is corrected.[66]

s) In patients who develop post-operative or post-hemorrhage related anemia, IV iron is recommended.[67,68]

t) 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 peri-operative thrombosis expert should be consulted. In some circumstances (such as proximal femur fractures), early surgical fixation even in the presence of anticoagulation results in the same or less blood loss while reducing hospital length of stay and peri-operative complications.[69-71]

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

v) When substantial blood loss is anticipated, acute normovolemic hemodilution should be considered.[72,73] In some populations where the patient may be hypervolemic (i.e. liver failure), hypovolemic phlebotomy and return of whole blood post-procedure also reduces the risk of receiving a blood transfusion.[74]

w) When substantial blood loss is anticipated or encountered, intra-operative cell salvage should be considered.[75]

x) 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.[76]

y) 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.

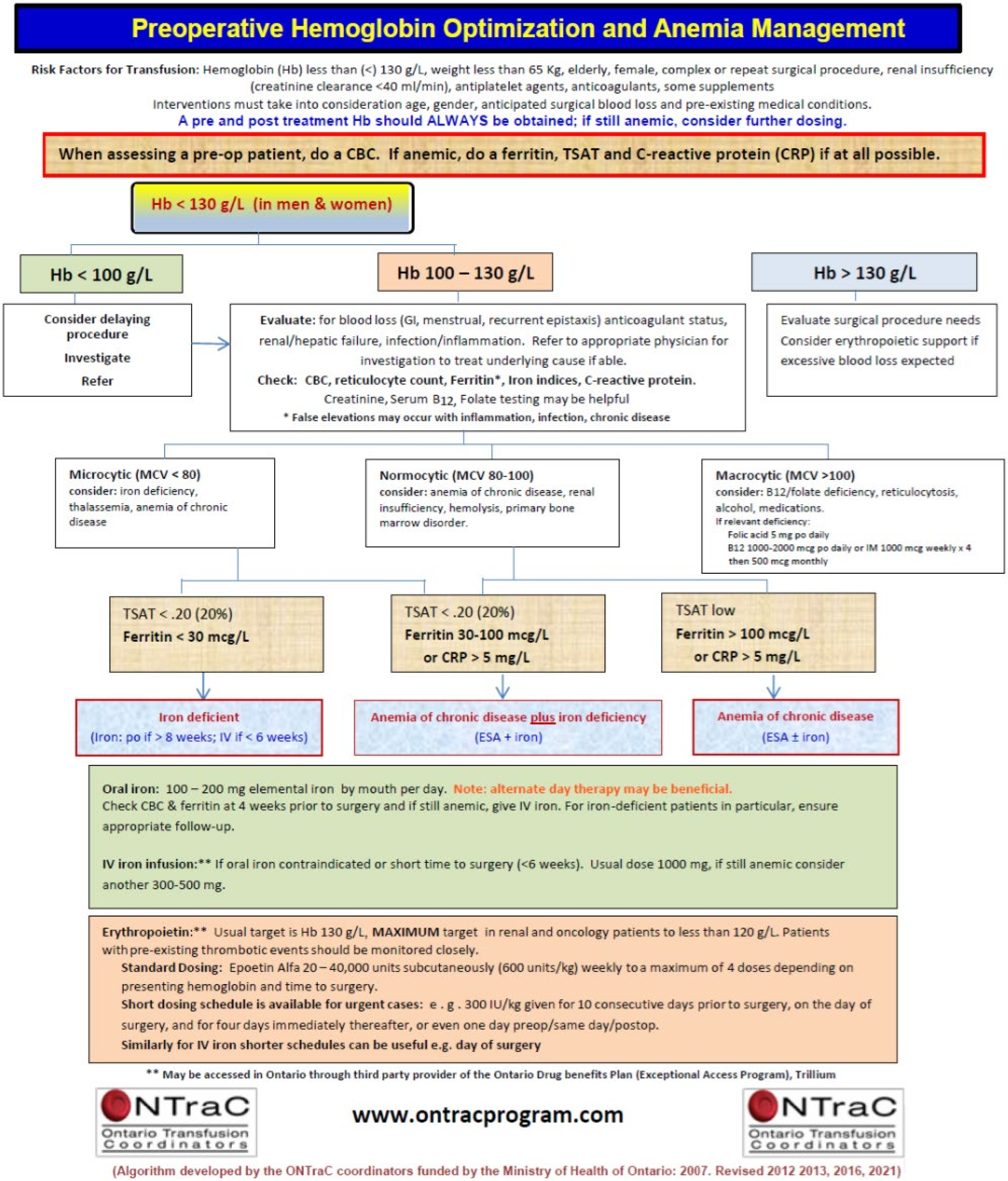
z) Coagulopathy encountered in the hemorrhaging patient should treat the underlying coagulopathy. Low calcium (ionized less than 1.15mmol/L or uncorrected calcium less than 2.14mmol/L) should be treated with intravenous calcium and retested. Fibrinogen should be replaced in accordance with current guidelines available from NAC.[77] The decision to use plasma or prothrombin concentrates should be made based on guidelines from NAC.[78] When a known isolated defect is present (such as antithrombin in cardiac surgery) replacement using the corresponding factor concentrate is preferable to plasma.

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 PBM program has the potential to improve outcomes and simultaneously reduce system costs. In the interest of improving care to its citizens, every province and territory should develop a PBM program.

Current clinical recommendations already exist, and examples are offered from ONTraC,[26] the American Society of Hematology,[79] and the Mayo Clinic[2]. For visualization purposes, see ONTraC's algorithm below (Figure 1).

A cost comparison using a single unit of RBCs in managing anemia is provided in Table 1 below. While transfusion of a single RBC unit may raise Hb 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.

Figure 1: ONTraC's Peri-operative Hemoglobin Optimization and Anemia Management algorithm.[80]



4.0 COST COMPARISONS

Table 1: Cost comparisons of anemia strategies.
See Appendix A: Table 1 & 2 Notes and Assumptions for additional information.

Intervention	Dose	Cost	Duration of Therapy	Peak Effect	Total Acquisition Cost	Additional Costs*	Change in Hb (g/L)	Cost per g/L Increase	Relative Cost per g/L Increase in Hb Compared to 1 Unit of RBC	Cost Comparator to 1 Unit of RBC**
Red Blood Cells	1 unit	$470.00	120 min x 1	End of infusion; shorter ½ life than endogenous cells	$470.00	$328.30	10	$79.83	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	0.08
Iron Sucrose	300mg	$112.50	90 min x 4	5-8 weeks	$450.00	$623.15	39	$27.52	0.34	1.34
Ferric Derisomaltose	1200mg	$540.00	60 min x 1	5-8 weeks	$540.00	$107.32	39	$16.60	0.21	0.81
Ferric Carboxymaltose	1200mg	$540.00	60 min x 1 + 30 min x 1	5-8 weeks	$540.00	$458.17	39	$25.59	0.32	1.25
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	0.82	2.54
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	1.76	2.54
Epoetin alfa (pre-op orthopedics)	20,000 units (300U/kg for 70kg) q daily	$285.00	1 min x 14 days	4-6 weeks	$3990.00	$268.94	7.3	$583.42	7.31	5.34

*Nursing, lab, testing, chair time, etc., (may vary). **Acquisition cost plus additional costs.

Table 2: Inflation cost of epoetin alfa.
See Appendix A: Table 1 & 2 Notes and Assumptions for additional information.

	Cost in 1998[81]	2026 Inflation Calculator[82]	2026 Actual Cost	% Difference from Expected Inflation
Epoetin alfa, 20,000 units	$267	$484.65	$325.09	67.08
Cost feasible epoetin alfa, 20,000 units (orthopedics)	$158	$286.80	$325.09	113.35
Cost feasible epoetin alfa, 20,000 units (cardiovascular)	$214	$388.45	$325.09	83.69
Red Blood Cells, 1 unit	$210	$381.20	$470	123.29

APPENDIX A: TABLE 1 & 2 NOTES AND ASSUMPTIONS

Notes:

Table 1: Cost comparisons of anemia strategies

- Increased hospital time, morbidity, and mortality associated with RBC transfusion are not considered in this table.
- A change in Hb does not imply equal efficacy. One unit of transfused RBCs temporarily improves Hb levels, but suppresses endogenous erythropoiesis, and cells are broken down more rapidly than endogenous cells. Conversely, endogenous RBCs produced with appropriate supplementation are expected to have a normal lifespan.
- Comparison of epoetin dosing on an accelerated daily schedule near the time of operation versus the weekly schedule for one month pre-operatively underscores the need for system design to allow for early intervention. Anemia management is more cost effective with six-week pre-operative planning. However, even a single dose of epoetin may be adequate to prevent the need for transfusion.[83]

Table 2: Inflation cost of erythropoietin

- While orthopaedic surgery is close to meeting the quality-adjusted life years cutoff defined in the 1998 Economic Evaluation of Erythropoietin Use in Surgery report,[81] cardiovascular surgery has already met the cutoff, moreover the cost increase of RBCs (123%) is nearly double that of the cost increase of 20,000 units of epoetin (67%).
- All dollar ($) values given are CAD.

Assumptions (Table 1 only):

General:

- All dollar ($) values given are CAD.
- Unless otherwise indicated in the sections below, the cost of:
  - Infusion chair time per minute = $0.71.
  - Nurse time per hour = $37.00.
  - Laboratory testing per infusion treatment cycle = $28.47.
  - Infusion set-up per infusion = $7.94.

Regarding red blood cells:

- Cost per one unit of RBCs was provided by Canadian Blood Services.
- One transfused unit of RBC raises Hb levels by 10g/L.[84]
- Additional costs of RBC administration in Canada have been estimated to total $243.10,[85] however these costs may be higher (up to $522.78).[86] To keep comparisons similar, the total additional costs for RBC administration was calculated as follows:

$$\$243.10 + (120min \times \$0.71) = \$328.30$$

Regarding oral iron salts (ferrous sulphate, ferrous fumarate):

- Cost per dose of iron salts was provided by a local pharmacy in Saskatchewan and is between $0.17-$0.28. The total acquisition cost was determined using the higher cost in this range and the duration of therapy is 20 weeks (14 weeks to improve Hb levels and an additional 6 weeks for iron stores).

- Anemia treatment with oral iron salts raises Hb levels by 28g/L.[87,88]

Regarding IV iron (iron sucrose, ferric derisomaltose, ferric carboxymaltose):

- There is 100mg of iron present in 200mL of whole blood, which equates to 30g Hb; in a 70kg adult with a blood volume of 70mL/kg, this rise equates to a 6.1g/L increase in Hb per 100mg of iron administered, but the effects are not linear.
- Additional costs for administration of each IV iron were calculated based off Canada's Drug Agency's Pharmacoeconomics Review,[89] specifically Table 10 of Appendix 5,[90] which considers further cost details such as the amount of attention required of nursing staff per type of infusion. Each was calculated taking into account nursing, infusion set-up, chair time and laboratory testing costs.
- The increase of Hb levels after the completion of therapy is between 32.9-45.8g/L.[91] The average, 39g/L increase in Hb, was used.
- Iron sucrose:
  - Per Canada's Drug Agency, the cost of iron sucrose is $37.50/100mg.[89]
- Ferric derisomaltose:
  - Per Canada's Drug Agency, the cost of ferric derisomaltose (referred to as iron isomaltoside by Canada's Drug Agency) is $45.00/100mg.[89]
- Ferric carboxymaltose:
  - Cost of ferric carboxymaltose was provided by Canada's Drug Agency Reimbursement Recommendation.[92]
  - The total dose for ferric carboxymaltose is 1200mg, but the maximum dose at one time is 1000mg resulting in two required visits. The first visit is approximately one hour in length, and the second is shorter.
  - For anemia treatment with ferric carboxymaltose there's significantly higher risk of hypophosphatemia.[93,94] To account for the cost of hypophosphatemia treatment, $272 was included in the additional cost calculation for ferric carboxymaltose. This was based off an Italian review that found that the costs for hypophosphatemia treatment and follow up to be €169 (approximately $272 at the time of writing) per patient treated with ferric carboxymaltose.[93] Additionally, a British review found that hypophosphatemia treatment and follow up to be £226 (approximately $414 at the time of writing).[94] A formal Canadian review has not been done, and Canada's Drug Agency did not evaluate this risk in their review.

Regarding epoetin alfa:

- Cost of epoetin alfa as per the Saskatchewan Drug Formulary is $14.25/1000U up to 20,000 units, and $12.17/1000U for 40,000 units.[95]
- Additional costs of epoetin alfa were calculated based off 30 minutes of nursing time and one minute of chair time per dose administered.
- Change in Hb in healthy patients is 31g/L with the dosing schedule of either 150U/kg three times/week or 40,000U/week.[96]
- Change in Hb in pre-operative orthopedics is 14.4g/L on average using 600U/kg/week and 7.3g/L on average using 300U/kg for 10 days pre-operatively, and 4 days post operatively.[96]

APPENDIX B: IMPROVING IRON ABSORPTION

Oral iron salts:

- Oral iron salts (gluconate, sulfate, fumarate, ascorbate, bisglycinate) are first line choices due to low cost and good efficacy.[97]
- Using a lower dose iron salt (40mg elemental iron or less) may reduce side effects compared to higher dose iron salts. In octogenarians, 15mg elemental iron is adequate given enough time.[98]
- Given twice the length of time, every other day dosing of an iron salt is as effective at correcting iron deficiency anemia as daily dosing.[99-104]

Comparisons to other oral iron supplements:

- Iron polysaccharide claims to have better gastrointestinal tolerance but has vastly inferior results at resolving iron deficiency anemia.[97] Gastrointestinal effects are similar or higher in some randomized control trials for iron polysaccharides.
- There is one case report involving a toddler with severe iron deficiency anemia where switching from Feramax (an iron polysaccharide) to Palafer (oral iron salt ferrous fumarate) resolved her anemia.[105]
- Comparative studies have been done with the following results:
  - NovaFerrum (iron polysaccharide) versus ferrous sulfate (oral iron salt): iron deficiency anemia resolution 6% versus 29%.[106]
  - Feramax (iron polysaccharide) versus ferrous fumarate (oral iron salt) versus ferrous ascorbate (oral iron salt): Hb change 3.56g/L versus 11.59g/L versus 17.14g/L.[107]
  - Niferex (iron polysaccharide) versus ferrous fumarate (oral iron salt): Hb change 6g/L versus 28.4g/L.[108]
- For dietary iron, heme iron is better absorbed (such as liver; 15-35% bioavailability) than non-heme iron (such as spinach; 1.4-7% bioavailability).[97]

Facilitators of iron absorption:

- The addition of vitamin C to iron salts does not improve iron absorption when ferritin is low,[109] but may facilitate iron utilization in the body especially when inflammation is present.[110] It may also improve absorption when higher levels of inhibitors (phytates, etc.) are present.[111]
  - Vitamin C aids in the conversion of ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}). Ferric iron is found in plants, but most iron supplements contain ferrous iron which is why no change is observed when adding vitamin C to iron salts. The addition of vitamin C may increase uptake in those who are strict vegetarians who do not take iron salts or in those who only supplement with “plant-based iron” such as Floradix.
- Additional nutrients present in food (especially heme sources such as vitamin A, zinc, copper, protein, and magnesium) may facilitate improved absorption.[112,113]
- Fermented foods increase iron absorption.[114]
- *Lactobacillus plantarum* (and *Bifidobacterium lactis*) as a probiotic supplement improves absorption and reduces gastrointestinal side effects.[114]
- Estrogen supplementation decreases hepcidin and may improve iron absorption.[115]

Inhibitors of iron absorption:

- Concomitantly consuming calcium, tea, coffee, eggs, soy, antacid/proton pump inhibitors, or foods high in phytates or oxalates (some vegetables and grains) decreases iron absorption.
- Energy (calorie) restriction and/or low carbohydrate diets decrease iron absorption.[116,117]
- Strenuous exercise (VO_2 max or equivalent training to failure) increases inflammation (and Interleukin-6 and hepcidin) and may interfere with iron absorption.[118-120] The timing in relation to exercise and time of day shows that iron is best absorbed in the morning and very shortly after exercise (hepcidin peaks three to six hours after exercise).[121] One hour of running has half the hepcidin elevation as two hours of running.[122]

APPENDIX C: PREVIOUS AUTHORS

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