

Management of Perioperative Anemia in Patients that Performed Abdominal Major Surgery

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Abstract

Introduction: Anemia is a recognized predictor of adverse postoperative outcomes in patients during abdominal major surgery. The management of perioperative anemia involves many strategies. Pre-operative anemia has adverse outcomes in major surgery and is called the fourth factor. Anemia was then classified into mild, moderate, and severe depending on hemoglobin level. It is present almost in 40% of patients that performed elective major surgery. Patients with preoperative anemia are associated with an increased rate of blood transfusion together with a risk for high morbidity and mortality. The most usual cause of preoperative anemia is iron deficiency, which can be treated with oral/intravenous iron depending on the time scheduled for surgery. A review concluded that anemia recovery earlier with preoperative intravenous iron than with oral iron supplement. A perioperative erythropoietin injection is also a reasonable approach for patients with hemoglobin between 10 and 13 g/dL and if autologous blood donation is performed. The protocol requires a baseline complete blood count and iron studies and all patients should receive iron supplementation during erythropoietin therapy. The next strategy is stabilized macro/ microcirculation to optimize the patient's tolerance to bleeding. Recent recommendation, in general, suggests no bridging therapy consider it only if high thrombotic risk. Finally, targeted surgery should be used to reduce intraoperative and postoperative bleeding. We recommend a restrictive transfusion strategy. Allogeneic blood transfusion is associated with an increased incidence of nosocomial infections. Postoperative anemia must be treated with the use of intravenous iron. We ought to know fresh frozen plasma used in deficit in factor V, XI, in dose 15-30ml/kg and be aware of its complications as immunomodulation, acute lung injury, and cardiac overload.

Conclusion: Our goal is to improve patients' clinical outcomes.

Keywords: anemia, blood, blood plasma, iron deficiency anemia, transfusion-transmitted infections.

Introduction

The objective of these papers is to provide the anesthetists and the surgeons with an overview of the perioperative anemia how to improved really clinical management of patients. As we know, the anemia in the abdominal surgical

patients has a significant impact on perioperative morbidity and mortality. Anemia is a health problem and is called the fourth factor that has to do with very low red blood cells or low hemoglobin. Hemoglobin is an iron-rich protein that binds to oxygen in the lungs and transports it to every tissue and cell. Global anemia rates are very high. According to World Health Organization a patient is anemic when the level of hemoglobin is under 13 g/dL in men, hemoglobin is <12 g/dL in women and when the hemoglobin is <11 g/dL in pregnant [1]. Anemia was then classified into mild when the level of hemoglobin < 12g/dL, moderate the level of hemoglobin < 10g/dL, and severe the level of hemoglobin < 7g/dL, depending of hemoglobin level.

On the basis of the level of hemoglobin anemia is divided into first grade anemia 11.5 g/dL: the level of hemoglobin is under 10 g / dL: is called second grade anemia (9-7 g / dL) and deep anemia (third grade) when the level of hemoglobin is less than 7 g / dL.

Another reference: Third degree anemia the level of hemoglobin 6.5-8 g / dL and fourth degree the level of

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hemoglobin $<6.5 \text{ gr/dl}^{-1}$ [2].

In an European study estimated the prevalence of preoperative anemia to be 31.1% in women and 26.5% in men. Anemia is associated with difficult outcome and need of blood transfusion especially during the SARS-CoV-2 pandemic that multiply the need for Perioperative Bleeding Management implementation [3]. Anemic patients very often presented to surgery without considered assessment and management of this risk factor for adverse clinical outcome [4]. The presence of anemia should be investigated in all major abdominal surgery with expected blood loss ($> 500 \text{ ml}$). When treating anemia pre-operatively, the target hemoglobin concentration should be $\geq 13 \text{ gr/dl}^{-1}$, in both sexes, to minimize the risk of transfusion associated different clinical outcomes [14].

There are a number of guidelines from professional associations recommending “what to do”.

In 2013, the European Society of Anesthesia realized guidelines for the management of severe perioperative bleeding and first update in 2016 with the additional information to assist the doctors to Prepare, Plan and take Action and made these guidelines the first on patient blood management that does it means “how to do”. The Patient blood management is a wide program aimed at minimizing the need for red cell transfusion and thus improving postoperative clinical outcome and reduced health care costs [4, 5].

Prepare

Prepare for any potential bleeding risks by performing preoperative assessments, particularly to detect anemia and allow time for its correction. Perioperative anemia increases the risk of numerous complications. Preoperative anemia has been shown to be a strong predictor for perioperative transfusion of allogeneic blood products such as Red Blood Cells, which itself carries a significant risk of different events and mortality [11]. Various strategies for the correction of pre and postoperative anemia have evolved. The implementation of a patient blood management program, which included patient assessment 4 weeks before surgery, was shown to be effective in reducing the rate of preoperative anemia [12]. Other groups have successfully used Patient Blood Management program ought to assess for anemia about 3-8 weeks before surgery. Assessment of patients 3 to 8 weeks before elective surgery provides enough time to initiate treatment and to take effect. This recommendation is also in agreement with current consensus and practical recommendations [5]. We need to identifying the cause (iron deficiency, renal insufficiency or inflammation). Anemia related to iron deficiency is common. Iron is the most common and widespread nutritional deficiency, even in industrialized countries, and affects about two billion people worldwide [8, 9]. Iron deficiency, with or without anemia, is associated with chronic conditions such as cancer (43% across malignances), inflammatory bowel disease (45%) [10].

Patient Blood Management program focus on three main “pillars” (first, optimization of hemopoiesis, through the interventions to increase hemoglobin concentration; second, minimizing blood loss and bleeding; and third, protect and optimize physiological tolerance of anemia) all of which have a preoperative, intraoperative and postoperative component [4]. Patient blood management has been shown to improve outcomes and reduce healthcare costs in a number of studies [4, 5]. Recent work shows how this systematic approach to optimizing hemoglobin in surgical patients has been effectively with improved 90-day postoperative outcomes in a United Kingdom center [13]. Anemia in surgical patients is a common and serious problem; around 40% of patients presenting for intermediate or major surgery are anemic [14]. Anemia is a recognized predictor of adverse postoperative clinical postoperative morbidity and mortality. All patients for elective surgery in whom blood loss is expected to be $> 500 \text{ ml}$ should have their hemoglobin checked pre-operatively and be investigated if they are found to be anemic. A recent systematic review found that anemic patients with rectal cancer have a worse overall survival and disease-free survival after receiving transfusion of blood. [15]. Transfusion of red cells is associated with increased all-cause mortality and cancer-related mortality [16] as well as increased recurrence of colorectal cancer [17]. Whether the relationship between anemia, red cell transfusions and morbidity/mortality is the cause is unknown. Detection of preoperative anemia should be carried out as soon as possible, at least 14 days before elective surgery [18] and preferably more than 30 days before surgery [21].

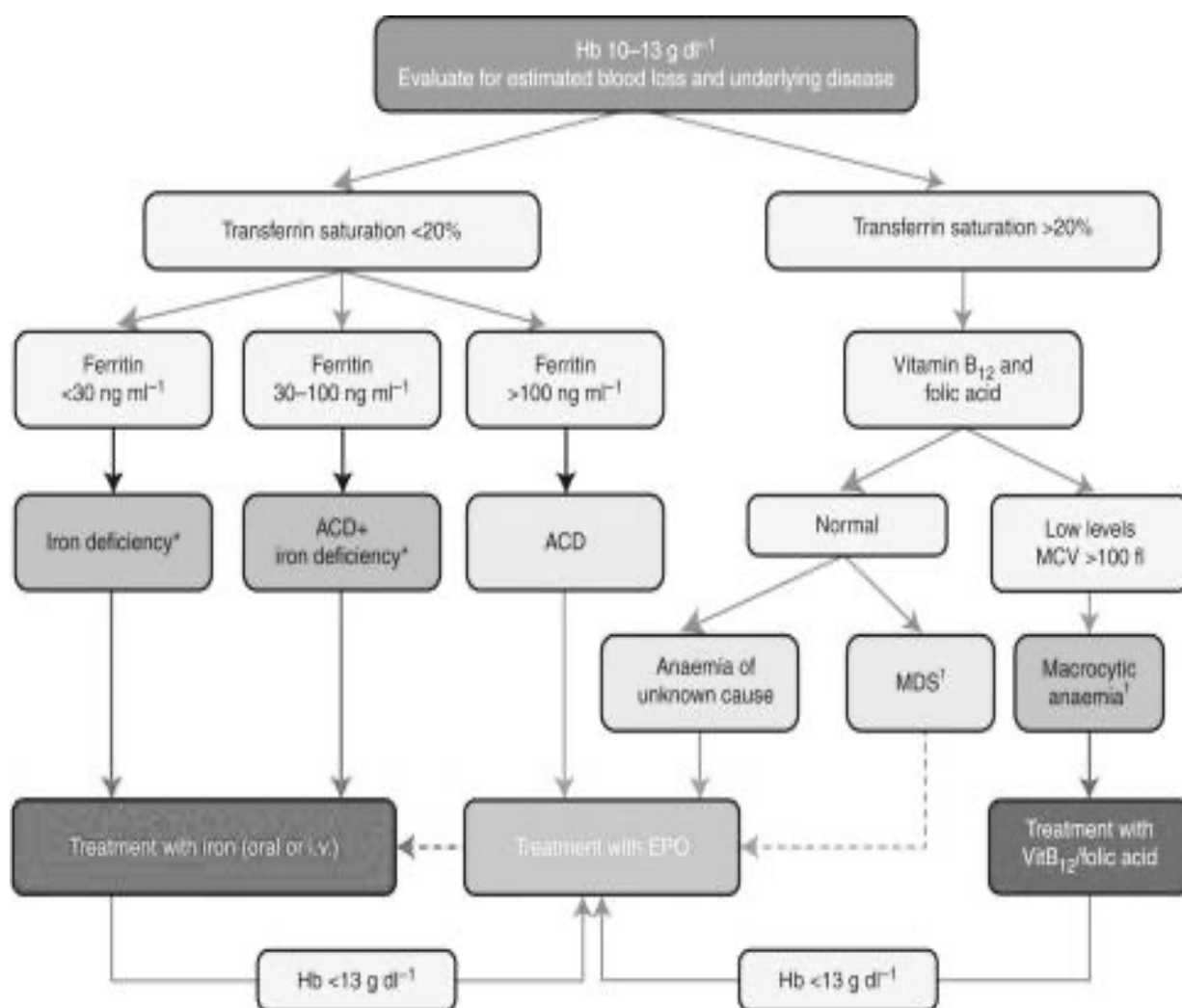
Many studies have shown an increase in hemoglobin and a decrease in red cell transfusion when iron deficiency anemia is treated with iron therapy [18]. Iron deficiency anemia is the most common type of anemia both worldwide [19] and in the surgical population [20]. If anemia (hemoglobin $< 130 \text{ gr/dl}^{-1}$) is suggested using point-of-care testing, laboratory testing should follow; further evaluation should include full blood count, serum ferritin, transferrin saturation, vitamin B12 and folate, a marker of inflammation (e.g., serum C-reactive protein) and a marker of renal function (e.g., serum creatinine) [5]. The most usual cause of preoperative anemia is iron deficiency, which can be treated with oral/intravenous iron depends of the time scheduled for surgery. A review concluded that anemia recovery earlier with preoperative intravenous iron than with oral iron supplement [21]. Oral iron supplementation may be suitable for a lot of patients, and any side-effects are usually mild [2, 3, 4]. When the time between consultation and surgery is sufficient, oral iron treatment may be considered. Oral iron replacement should be targeted to patients with iron deficiency with or without anemia whose surgery is scheduled 6–8 weeks after diagnosis, preferably by the primary general physician. Daily (40–60 mg) or alternate-day (80–100 mg) treatment with oral iron and nutritional advice should be initiated immediately in patients with iron deficiency and no contra-indications [5]. Oral

iron is cheap and both oral and intravenous iron increase hemoglobin concentration, whereas diminish the need for red cell transfusion. According to literature it seems that oral iron increase hemoglobin $\sim 5,15 \text{ g dl}^{-1}$ within 30 days therapy [5].

At that large period of treatment is required for oral iron more side-effects occur. Gastro-intestinal side effects might lead to poor compliance with oral iron treatment. In our ward, monitoring of efficacy for oral iron is recommended after 4 weeks of treatment. A systematic review concluded that patients with preoperative iron deficiency anemia may have an earlier and more robust recovery of hemoglobin concentration with preoperative intravenous iron than with oral iron supplementation [5, 14, 24].

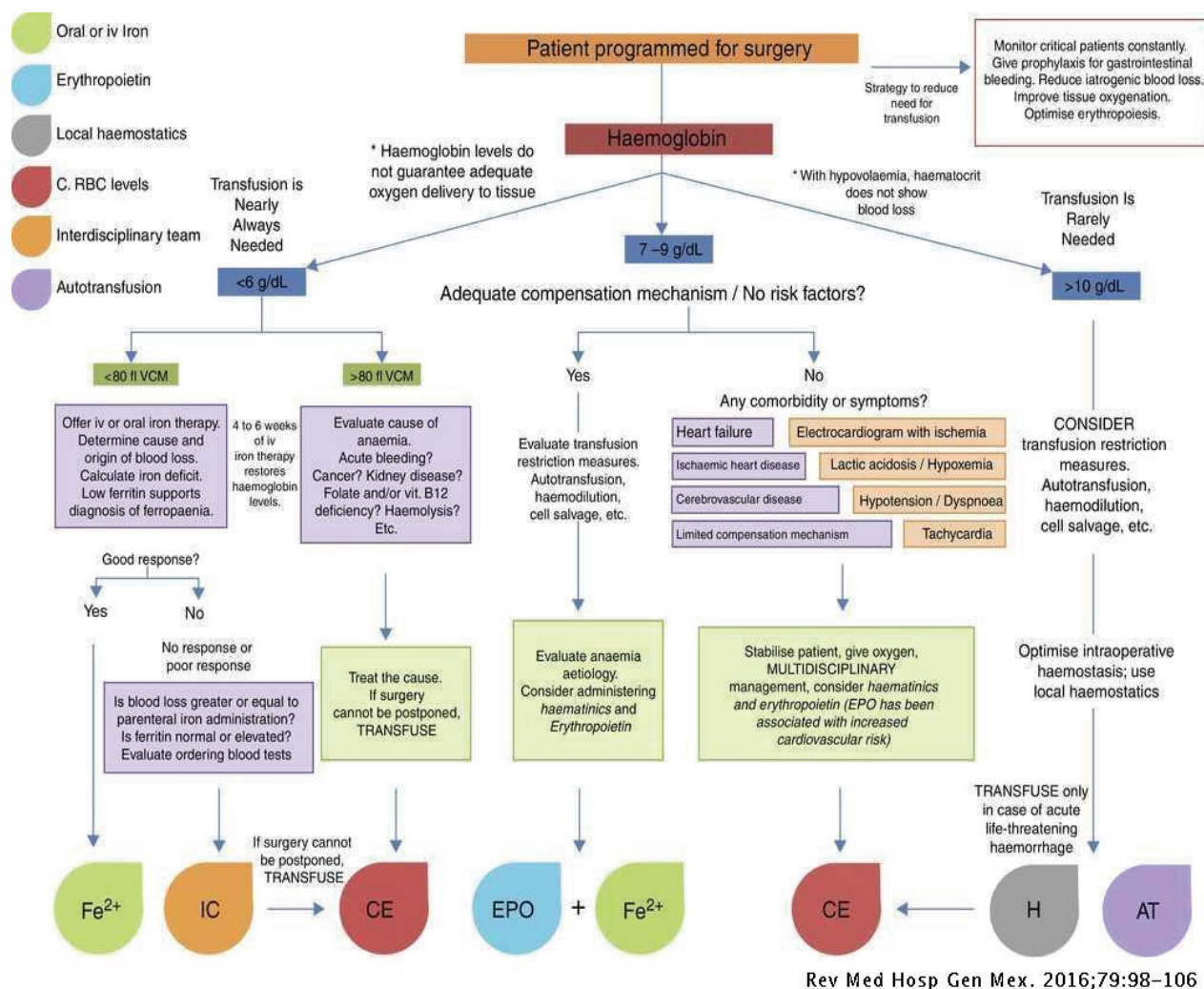
Intravenous iron should be used as front-line therapy in patients who do not respond to oral iron indicated if oral iron is poorly tolerated from the patient, is ineffective (no increase in hemoglobin after 4 weeks), if the major abdominal surgery is scheduled for < 6 weeks after the diagnosis of iron deficiency, or in case of functional iron

deficiency [2, 5, 24]. Single dose of intravenous iron seems to increase hemoglobin $> \text{hb} \sim 1.8 \text{ g dl}^{-1}$. Intravenous iron is recommended by many clinical guidelines based largely on its effectiveness in reducing anemia. However, the association with important safety outcomes, such as infection, remains uncertain [22]. Iron supplement dosage is based on a formula used to calculate total iron deficiency [iron deficiency = (target Hb – actual Hb) $\times 2.4 \times \text{kg weight} + 500$] and on the cause of chronic iron loss [24]. Adjuvant therapy with erythropoiesis stimulating agents such as erythropoietin improves the effectiveness of iron therapy and reduces dose requirements. Actuality has shown that intravenous iron with or without adjuvant erythropoietin can reduce the need for transfusion in surgical patients. Perioperative erythropoietin injection is also a reasonable approach for patients with a hemoglobin between 10 and 13 g/dL and if autologous blood donation is performed. The protocol requires a baseline complete blood count and iron studies and all patients should receive iron supplementation during erythropoietin therapy [Figure nr1 and nr 2] [14,



ACD, anaemia of chronic disease; EPO, erythropoietin; MCV, mean corpuscular volume; MDS, myelodysplastic syndrome.

Figure 1 Protocol of patient blood management



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Figure 2 Algorithm for patient blood management on surgical ward

24]. Patients should receive erythropoietin injections on preoperative days 21, 14, and 7. Their last dose of erythropoietin should be on the day of the surgery [4, 5]. However, chronic use of erythropoietin is associated with thrombotic cardiovascular events in cardiac and/or renal failure patients [25, 26].

A documented clinical history and totally physical examination are needed to determine potential risk factors for decompensation, bleeding or thrombosis. Particular attention should be paid to the patient's personal and family history. The European Society of Anesthesiology (ESA) strongly supports the development of high-quality, evidence-based clinical practice guidelines to help standardize the approach to patient care and to improve overall clinical practice.[27]

ESA recommends the use of standardized questionnaires on bleeding and drug history as preferable to the routine use of conventional coagulation screening tests such as activated partial thromboplastin time (APTT), international normalized ratio (INR) and platelet count in elective surgery. For the medications that affect hemostasis ESA recommends that aspirin therapy should continue perioperatively in most

surgical settings. Where aspirin withdrawal before surgery is considered, ESA recommends a time interval of 3 days for all procedures where there is a very high bleeding risk. For intraoperative or postoperative bleeding clearly related to aspirin, it suggests that platelet transfusion be considered [5]. Minimum preoperative withdrawal for clopidogrel or prasugrel is 5 days in hemorrhagic risk for surgical patient while in high hemorrhagic risk for surgical patient will stop 7 days before. It suggests that the first postoperative dose of clopidogrel or prasugrel should be given no later than 24 h after skin closure.

We also suggest that this first dose should not be a loading dose. ESA recommends assessment of creatinine clearance in patients receiving direct oral anticoagulants (DOACs) who are scheduled for surgery. For intermediate and high bleeding risk procedures it recommends that rivaroxaban, apixaban and edoxaban should not be given for 2 days before the procedure (i.e., last oral intake 3 days before), pending a creatinine clearance (Cockcroft–Gault formula) above 30 ml min⁻¹ till 4 days before the procedure (i.e., last oral intake 5 days if the creatinine clearance is between 30- and 50-ml min⁻¹). Recent recommendation suggests no bridging

therapy. [5] According to Vitamin K antagonists (VKAs) ESA recommends that for low or moderate thrombotic risk patients [e.g., atrial fibrillation patients with CHADS2 score 4; patients treated for >3 months for a nonrecurrent venous thromboembolism (VTE)] undergoing procedures requiring INR less than 1.5, VKA should be stopped 3 to 5 days before surgery (acenocoumarin, warfarin). No bridging therapy is needed. Measure INR on the day before surgery and give 5mg oral vitamin K if INR exceeds 1.5. ESA recommends bridging therapy for high thrombotic risk patients (e.g., atrial fibrillation patients with a CHADS2 score >4; patients with recurrent VTE treated for less than 3 months; patients with a prosthetic cardiac valve). Warfarin: last dose 5 days before surgery; 4 days before surgery, no heparin; 3, 2 and 1 day before surgery, LMWH (last dose 24 h before surgery) SC daily; day 0, surgery. Acenocoumarin: 3 days before surgery, last dose; 2 and 1 day before surgery, same protocol as for warfarin. ESA suggest that the therapeutic dose of LMWH should be tailored for each patient, depending on the respective thrombotic and bleeding risks [5].

Plan

Plan for any intraoperative bleeding that may occur by using transfusion algorithms that incorporate pre-defined transfusion triggers to help guide hemostatic intervention, by being aware of the limitations of standard coagulation tests and by modifying the approach accordingly to use point-of care testing and others [5]. Perioperative bleeding management is a complex and changing field requiring multiple assessments and appropriate strategies to optimize patient care. There is an ongoing drive to find new alternatives to transfusion, a desire to reduce unnecessary use of blood products and a focus towards more evidence-based perioperative practice. Transfusion of RBCs is required only when the hemoglobin concentration decreases to levels at which overall nutrient demands cannot be met. The current mainstay of management for anemia in the older surgical patient, allogenic blood transfusion, can contribute to negative outcomes and is increasingly avoided where possible. Physicians are often asked to advise on

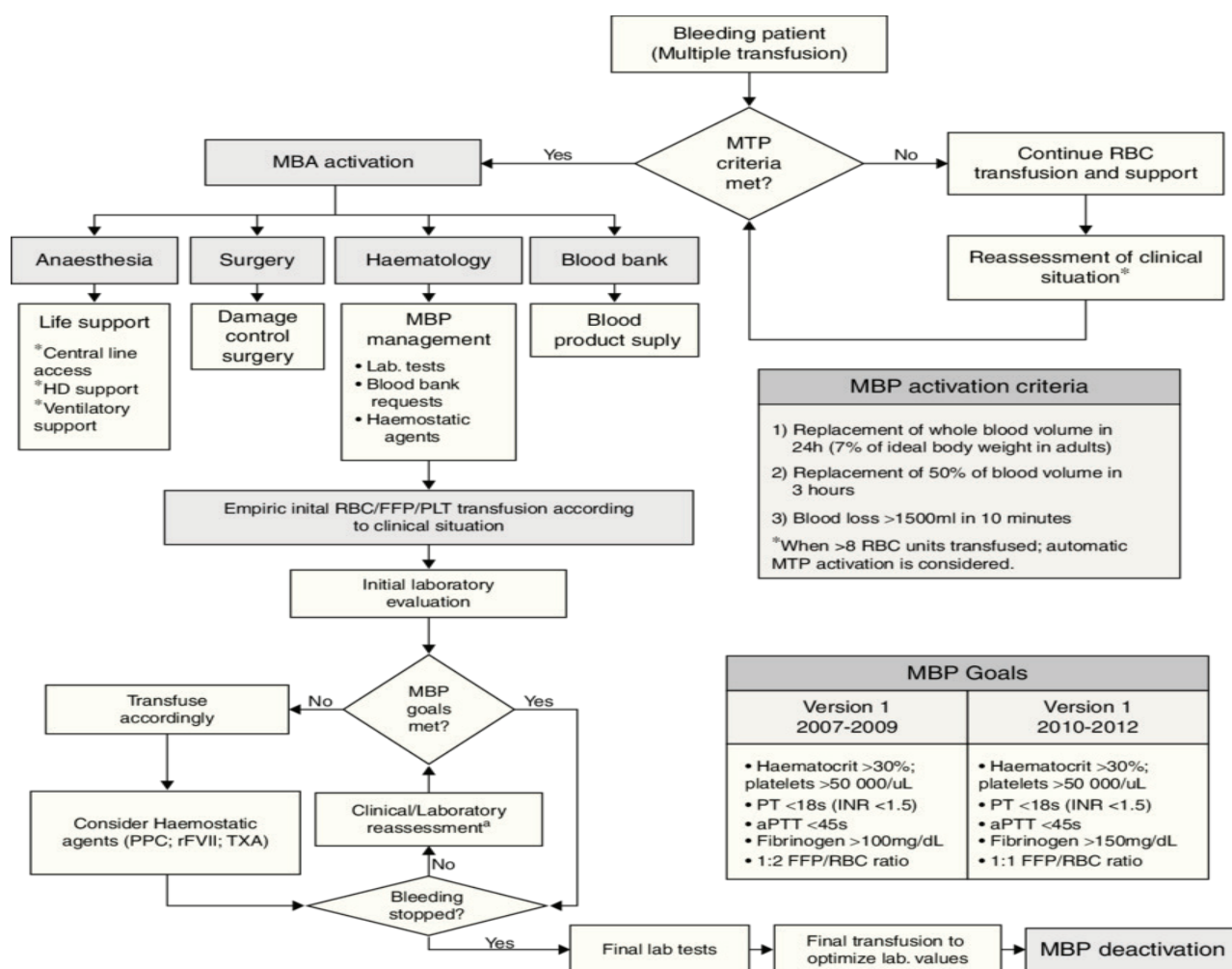


Figure 3. Massive transfusion protocol (MTP) algorithm. The boxes show the MTP activation criteria and MTP goals, used within the algorithm. RBC: red blood cells; FFP: fresh frozen plasma; PLT: platelet units; ICU: intensive-care unit; PT: prothrombin time; aPTT: activated partial thromboplastin time; PPC: prothrombin complex concentrate; rFVII: recombinant factor VII; TXA: tranexamic acid.

optimizing anemic patients preoperatively. The advice provided varies widely between physicians and anesthetists or surgeons managing the same patient group. All those involved in preoperative optimization and postoperative management of older surgical patients should ensure that a considered and consistent approach to anemia is part of routine management. Allogeneic transfusion is emerging as a risk factor for many common complications in transfused patients, such as pulmonary lesion and hospital-acquired infection, and is a predictor of morbidity and mortality in critical patients. As a result, the notion of blood transfusion as a revitalizing treatment capable of improving a patient's overall status and speeding up recovery has been replaced by the more rational view that use other, less risky, methods must be used [4-10].

Action

If potential bleeding risks are known in advance and a plan of treatment is in place, the necessary Action can be set in motion as required [5]. In elective procedures with high risk of blood loss and need for transfusion, preoperative autologous donation can be considered. Elective surgery offers the potential for preoperative optimization of hemoglobin levels before undergoing surgery. In this procedure, a few units of the patient's blood are collected when is possible before surgery and reinfused to the patient perioperatively if needed. Patient blood management strategies during surgery generally focus on minimizing blood loss and improving tolerance of anemia. Vital signs should be closely monitored, and unnecessary hypovolemia and tachycardia should be avoided. Various options are available to limit blood flow to the site of surgery, thereby limiting blood loss: improving intraoperative hemostasis at the site of bleeding are: electrocautery and argon-beam coagulation, for cleaner cuts together with more effective hemostasis; topical hemostatic agents containing a mixture of thrombin, fibrinogen, calcium, collagen, gelatin, and cellulose act as a fast acting tamponade patient positioning to elevate the site of surgery, use of tourniquet, embolization or infusion of local vasoconstrictive agents. Hypotensive anesthesia is another approach to limiting blood loss, although hypotension must be closely monitored by a team of experienced anesthetists to ensure adequate perfusion of vital organs.

Another systemic approach to minimizing blood loss is to avoid hypothermia as hypothermia can adversely affect platelet function [24]. Surgery in cancer patients is challenging in both medical and transfusion terms. Surgery is usually more invasive, the surgical site is usually highly vascularized, and the clinical characteristics of the patients are far from ideal (preexisting anemia, advanced age, malnutrition, comorbidities, etc.). Because of this, indications for transfusion in these patients are less clear, and rely more on the experience of the surgeon than on guidelines. Massive bleeding affects delivery of blood to

organs and tissues (due to hypovolemia), as well as the oxygen carrying capacity of blood (due to anemia) [5]. For any intraoperative bleeding first of all we need to utilizing transfusion algorithms. Transfuse of RBCs performed only when is really necessary, is required only when the hemoglobin concentration decreases to levels $< 7\text{g dL}^{-1}$. ESA recommends a restrictive transfusion strategy which is beneficial in reducing exposure to allogeneic blood products [5]. In these cases, fresh whole blood is essential for oxygen transport and adequate coagulation, since studies have shown that storing whole blood interferes with the metabolism, biochemistry, morphology and activity of red blood cells, and therefore affects the quality of the blood. It has also been reported that the longer the blood is stored, the greater the detrimental effect on coagulation [5, 24].

Although contamination of blood components with infectious agents represents a continuing challenge in transfusion medicine, rates of infection with known blood transmitted pathogens (e.g., HIV, HBV, HCV) are low following the implementation of high sensitivity testing methods. However, (re-) emerging pathogens remain a concern. Leukodepletion refers to the process of removing white blood cells from a unit of RBCs or platelets to a standardized degree. This is accomplished through either removal of the buffy coat following centrifugation or pre-storage filtration. The current consensus is that leukodepletion has defined indications in the prevention of three complications of blood transfusion: febrile non hemolytic transfusion reactions (HTRs), platelet refractoriness due to alloimmunization to human leukocyte antigen and transmission of cytomegalovirus. Leukodepletion process has been shown to be effective clinically and in cost too [29]. Clinically, leukodepletion might reduce the transmission of Creutzfeldt–Jacob disease and on the basis of accumulating evidence of leukocyte-mediated transfusion-related immunomodulation [30]. ESA recommends early and targeted treatment of coagulation factor deficiencies in the plasma. Sources of coagulation factors are coagulation factor concentrates, cryoprecipitate or high volumes of plasma, depending on the clinical situation, type of bleeding, type of deficiency and resources provide. Anesthetist and surgeon ought to know that fresh frozen plasma used in deficit in factor V, XI, in dose 15-30ml/kg and always be aware of its complications as immunomodulation, acute lung injury and cardiac overload.

Finally targeted surgery should be used to reduced intraoperative and postoperative bleeding.

Conclusions

Management of perioperative anemia in patients that performed abdominal major surgery presents different challenges. Despite these challenges, evidence is emerging for methods of “transfusion sparing” intervention in order to optimize patients in the perioperative period. Given the current literature, we recommend employing patient blood

management programs incorporating the ESA guidelines when assessing patients prior to elective surgery and the use of intravenous iron possibly with the addition of erythropoietin in the management of anemic abdominal surgical patients.

Such interventions could be employed using guidance from the PBM approach. More research is required into the methods of optimization in the anemic surgical patient, in order to provide definitive answers. Perioperative bleeding management is a wide concept that requiring multiple data and appropriate ways to realize patient care. Patient blood management is a program to the individual patient aimed at minimizing the donor for red cell transfusion and thus improving postoperative outcomes [3, 5]. The diagnosis and treatment of anemia and iron deficiency should commence as early as possible in the peri-operative period, and ideally as soon as the decision to undertake surgery is made. Major abdominal surgery should not be postponed to allow the diagnosis and treatment of anemia and iron deficiency. Sufficient data exist to support intravenous iron as efficacious and safe.

Many strategies to improve transfusion safety are recommended. The useful strategy is stabilized macro/microcirculation that optimize the patient's tolerance to bleeding. ESA recommends a restrictive transfusion strategy which is beneficial in reducing exposure to allogeneic blood products. It recommends pathogen inactivation for fresh frozen plasma (FFP) and platelets, that labile blood components used for transfusion are leukodepleted.

ESA recommends that blood services implement standard operating procedures for patient identification and that staff be trained in early recognition of, and prompt response to, transfusion reactions. Our goal is to improve patients' clinical outcome and to reduce the mortality.

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