Interdisciplinary Recommendations for the Management of Anaemia (patient blood management)

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Introduction

The frequency of anemia is high along the perioperative treatment pathway (1). Since preoperative anemia is a predictor of morbidity and mortality in patients undergoing surgery with a risk of bleeding (2-4) and for the allogeneic blood transfusion rate (5), differential diagnostic workup of anemia and targeted therapy are regarded as measures to increase patient safety.

Although correction of low hemoglobin levels by the transfusion of red cell concentrates (RCCs) is indeed suitable for correcting laboratory values and possibly for improving oxygen supply of the patient in cases of acute anemia, it does not reduce the perioperative risk. On the contrary, allogeneic blood transfusion is itself associated with a worse outcome (6,7), and even with use of those blood products available in Austria which meet the requirements of optimal blood use (8), these risks still exist. Furthermore, blood products are a life-saving resource, for example in oncological patients, and should therefore not be administered inappropriately in the operating-theatre setting. In light of anticipated demographic trends with a decrease in the donor population and a rise in those requiring transfusion, the appropriate use of blood products will become increasingly important in the future.

Other measures are therefore required to avoid pre-, intra- and postoperative anemia, correct its underlying causes and optimize the patient's physiological tolerance of anemia. For the purpose of this management packet, the World Health Organization (WHO) has included the term "Patient Blood Management" (PBM) in its resolution WHA63.12 (9). In the German-speaking countries, this has been translated into the equivalent of "Anemia Management" or even "Patient-oriented Blood Management" (POBM); terms which are also understandable to lay people.

Even if the recommended individual measures during the perioperative management of anemia (10) do appear trivial and although there are pioneers in the implementation of PBM in, for example, Western Australia (11), the management concept still has not been applied nationwide in Austria. On the contrary, benchmark studies demonstrate a high incidence of preoperative anemia which had presumably not even prompted preoperative correction, but resulted instead in allogeneic blood transfusions being given, which, in the examined hospitals, were inhomogeneous for the selected procedures and high in number by international comparison (12).

One reason for the difficult implementation of the comprehensive anemia management program could be that doctors lack awareness of the risks and costs arising from anemia and allogeneic blood transfusions and so far there has been no consensus on the measures for anemia management by all of the medical faculties responsible for perioperative patient care. This interdisciplinary recommendation is designed to demonstrate practicable and evidence-based recommendations regarding perioperative anemia management of adult patients in terms of integrated care and to develop measures to implement them. Such an anemia management program is not intended to be undertaken in individual centers of excellence, but should benefit as much as possible all surgical patients in Austria. It should be possible at a later time to quantify the result of this Austrian consensus based on the improvement in treatment quality and outcome of patients with pre-, intra- and postoperative anemia and on the reduction of costs in the health service.

Methodology

In August 2011, scientific learned societies (LS) with competency in, and responsibility for, the perioperative treatment pathway (surgery, orthopedics, traumatology, internal medicine, hemato-oncology, general medicine, laboratory medicine, clinical pharmacology, transfusion medicine) were invited to collaborate in the interdisciplinary recommendation on the initiative of the Austrian Society of Anesthesiology, Resuscitation and Intensive Care Medicine. Every invited LS agreed to collaborate.

In addition, an interprofessional working group (IWG) of the medical consensus group was made available to provide advice. This comprised representatives of patients, patient ombudspersons and the Austrian Red Cross. The Vienna Association of Hospitals was co-opted for the planned implementation of the current recommended action in a pilot project ("Reform Pool Project").

At the first meeting of the working group in December 2011, the formulation of relevant clinical questions from the perspectives of various experts was laid down to form the basis of the interdisciplinary recommendation. Once these clinical questions had been formulated by the individual LS and gathered together, they were categorized in a second step by all those involved into those which were to be processed in the current version and those which were only to be considered at a later, planned revision. A further process categorized whether those clinical questions with a high priority had already been dealt with in available international recommendations or not. If available, then these international recommendations, e.g. the European Society of Anaesthesiology (ESA) guidelines (13), should be reviewed for their feasibility in the Austrian health care system and adapted where appropriate. If omissions are found in the work by international recommendations, then the clinical questions should be answered based on expert consensus if clinical studies are not available, or a systematic review should be undertaken for selected questions of high relevance, when study data are available. In February 2012, the Paracelsus Private Medical University in Salzburg was entrusted with the systematic review after obtaining and comparing the three cost estimates submitted by different evidence-based medicine (EBM)institutes in Austria. At the agreed date of completion in June 2012, delivery of the report on the results was unilaterally cancelled due to personnel changes in Salzburg. Subsequently, up-to-date cost estimates were recently obtained after purchase order processing at short notice and, in July 2012, the Department for Evidence Based Medicine and Clinical Epidemiology of the Danube University of Krems was entrusted with the agreed completion of the GRADE evidence profiles, including explanatory notes, by December 2012 (14).

It is intended to publish the collective consensual recommendations of the interdisciplinary working group on anemia management on the websites of the involved LS and in a printed version in a peer-reviewed medical journal. Furthermore, dissemination of the recommendations is planned through communication via the co-opted non-medical working group. In February 2012, the Federal Ministry of Health held out the prospect that the medical recommendations of the interdisciplinary working group would be incorporated in new nationwide guidelines; presentation of the final interdisciplinary recommendations are due in June 2013. The present project is the logical continuation of the Federal Quality Guideline on Preoperative Diagnostic Tests from 2011 (15) inasmuch as that before, during and after major procedures (with a risk of

bleeding) trans-sectoral diagnostic and therapeutic processes are to be triggered, essentially determined on the basis of a preoperative laboratory finding (full blood count).
The application for inclusion of the POBM program in the priority catalogue of the health reform was put forward in June 2013.

Results and their interpretation

The interdisciplinary recommendations refer to patients who undergo a planned major procedure (with a risk of bleeding) (15).

1. Preoperative correction of anemia:

Diagnostic investigations – Risk stratification – Stimulation of erythropoiesis

Perioperative anemia is an independent risk factor in surgical medicine and the most important predictor of the need for blood transfusion. The preoperative treatment of chronic anemia can reduce these risks.

1. The definition of anemia from the World Health Organization (WHO) is used for the diagnosis of preoperative anemia (males < 13 g/dL, females < 12 g/dL).
Approval: 10 LS + 4 IWG

Borderline levels between mild, moderate and severe anemia cannot be defined with accuracy. Furthermore, there is no risk stratification between the different preoperative degrees of anemia with respect to the postoperative outcome. Levels under the lower limit should be regarded as the trigger for correcting anemia and optimization above the lower limit of the WHO definition as the therapeutic goal.

Clinical question: Which minimal laboratory tests are necessary for the diagnostic workup of the primary cause of anemia and when?

Based on a body of evidence of moderate quality, the laboratory tests to diagnose anemia and suitable therapeutic measures for its correction result in a reduction of blood transfusions (systematic review 2012, Danube University of Krems[14]). It has not been possible to discover other patient-relevant outcomes using the currently available studies of low or very low methodical quality.

2. If anemia has been detected, then a preoperative diagnostic workup of its cause is recommended (e.g. iron deficiency, renal failure, inflammation).
ESA grade of recommendation 2013: 1C
Approval: 10 LS + 4 IWG

3. A practicable algorithm is recommended for the detection of iron deficiency anemia (Fig. 1).
Approval: 10 LS + 4 IWG

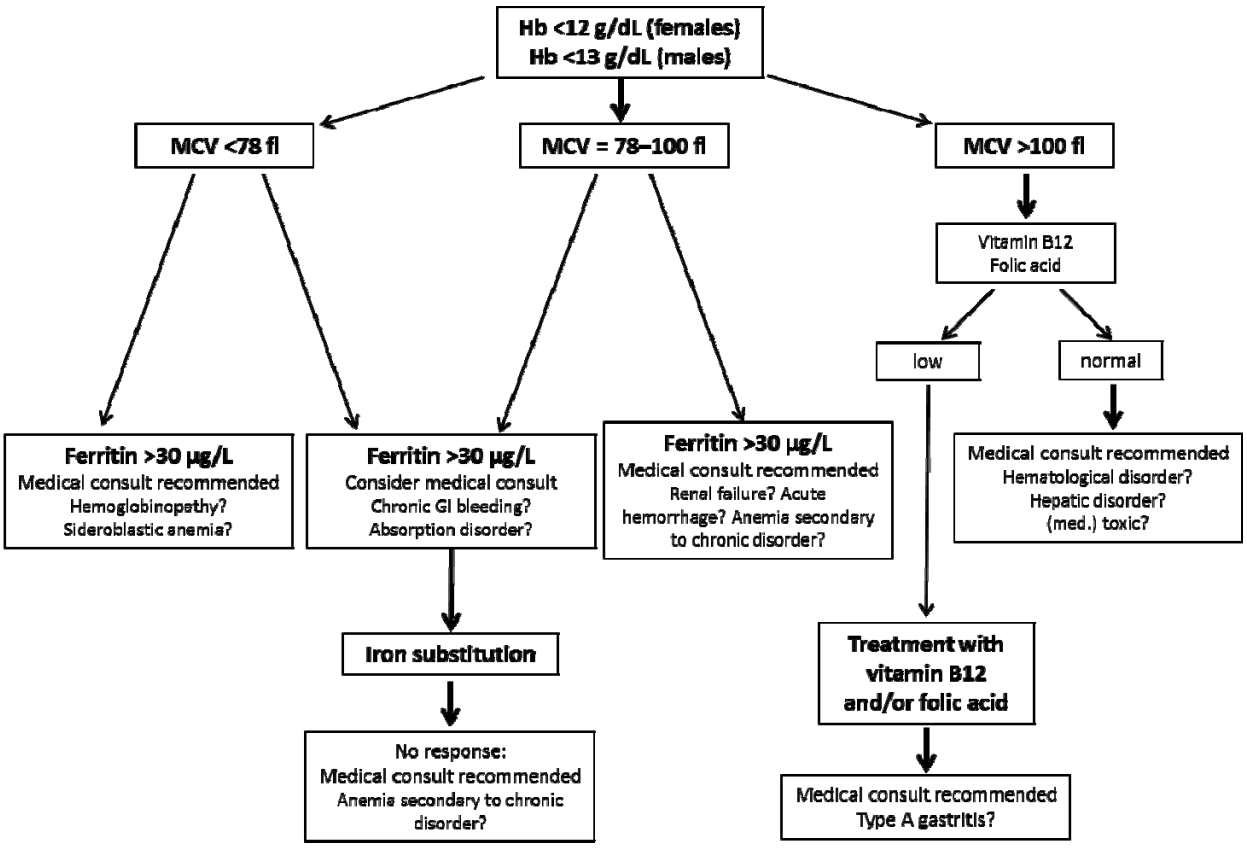

Fig. 1. Simplified algorithm for the diagnostic workup of perioperative anemia with therapeutic consequences. Modified according to (16,17)

Depending on the results of the full blood count, the following additional laboratory tests for the diagnostic workup of the cause of anemia are necessary as a minimum: Ferritin or vitamin B12/folic acid (repeated renal function parameters).

Since the laboratory tests require patient co-operation and time, the possibilities of promoting patient compliance and adherence should be dealt with by the working group and the co-opted working group. This includes patient information on the websites and in the brochures of the LS, as well as continuing medical education for those disciplines which carry out preoperative diagnostics according to the Federal Quality Guideline (BQLL) (15), or are incorporated as consultants for laboratory tests.

4. The point in time of the preoperative diagnostic investigations, including anemia diagnostics, should be sufficiently (at least six weeks) in advance of any elective procedure with a risk of bleeding.

ESA grade of recommendation 2013: 1C

Approval: 10 LS + 4 IWG

A time interval of more than four weeks is most likely to allow correction of diagnosed iron deficiency anemia (e.g. by oral administration of iron).

Clinical question: *Is a branching algorithm for the individualized correction of anemia, including combination therapy, appropriate before surgery or is the preoperative prescription of iron substitution sufficient for every patient?*

Iron deficiency anemia is a common form of chronic anemia. However, since the causes of anemia are manifold and iron deficiency is not always present, the blind prescription of iron is not always successful and the side effects and contraindications to iron administration should be considered. So on the whole, an individualized pathway is recommended for patient optimization (Fig. 1).

5. Iron deficiency anemia should be corrected by iron substitution prior to surgery.

ESA grade of recommendation 2013: 1B

The type of iron substitution is governed by the time window before the operation. Correction of perioperative iron deficiency anemia can be achieved more rapidly by intravenous substitution than by oral administration.

Approval: 10 LS + 4 IWG

6. Anemia of other origin, hemoglobinopathies and the cause of a presenting iron deficiency should be clarified by a diagnostic workup and appropriate therapeutic measures should be taken.

Approval: 10 LS + 4 IWG

The quality of the evidence for the exclusion of severe undesired side effects and increased mortality secondary to iron substitution is poor, but in the best evidence available there are no indications of increased tumor progression as a result of the perioperative administration of iron (systematic review 2012, Danube University of Krems [14]; ASH/ASCO-Guideline [16,17]).

7. There is no contraindication for iron substitution in cases of tumor diseases associated with concomitant iron deficiency anemia. An individual benefit-risk assessment is recommended (systematic review 2012, Danube University of Krems [14]; ASH/ASCO-Guideline [16,17]).

Approval: 10 LS + 4 IWG

Clinical question: *Which findings should be followed-up prior to elective surgery in patients previously diagnosed as anemic?*

8. The efficacy of measures to correct preoperative anemia should be confirmed prior to elective surgery by means of a full blood count.

Approval: 10 LS + 4 IWG

Since anemia is a perioperative risk factor, then postponement of the surgery date should be considered for the sake of patient safety if the targets are not met (correction of anemia = risk reduction).

9. The following key figure could be used prospectively nationwide to document the target improvement goal:

Anemia at the start of surgery: Percentage of patients (procedure-related)
Approval: 10 LS + 4 IWG

2. Avoidance of hemorrhagic anemia

Loss of red blood cell mass secondary to traumatic or surgical hemorrhage may be aggravated by concomitant coagulopathic hemorrhage. The acquired coagulation disorder is associated with blood loss, the need for blood transfusion, complications and mortality (13).

General measures to reduce intra- and postoperative hemorrhage

During procedures with a risk of bleeding, surgical hemostasis, general measures to promote hemostasis and mechanical autologous transfusion form the basis for POBM.

Clinical question: Which surgical measures can be recommended for meticulous hemostasis?

10. The following surgical measures can be recommended as examples of meticulous hemostasis and avoidance of hemorrhagic anemia (depending on the surgical site and type of surgery and individual benefit-risk assessment):
Exact surgical hemostasis and atraumatic dissection
Tourniquet
Pressure dressing
Local cryotherapy
Avoidance of suction drains
Approval: 6 LS + 4 IWG
Abstention: 4 LS

Clinical question: Which measures can be recommended for the non-specific optimization of clotting?

11. Maintenance of normothermia or correction of hypothermia is recommended as a non-specific concomitant perioperative measure in procedures with a risk of bleeding.
ESA grade of recommendation 2013: 1B
Correction of acidosis is recommended prior to procoagulant therapy with coagulation factor concentrates.
ESA grade of recommendation 2013: 1C
Correction of hypocalcemia should be initiated in cases of severe hemorrhage.
ESA grade of recommendation 2013: 2B
Approval: 7 LS + 4 IWG
Abstention: 3 LS

In the Austrian Structural Healthcare Plan (ÖSG 2012), the availability of non-invasive warming systems in hospitals providing specialized and centralized medical services has been defined as an infrastructure requirement.

Clinical question: Does autologous cell salvage reduce the amount of transfused allogeneic blood?

12. The salvage, processing and reinfusion of washed wound blood is recommended because this reduces allogeneic blood transfusion rates, especially in cardiac surgery, surgery of the great vessels and in major orthopedic surgery.

(ESA grade of recommendation 2013: 1A)

Autologous cell salvage may be considered for abdominal surgery, provided bowel contents have been initially discarded via a separate suction device and a broad-spectrum antibiotic has been administered.

ESA grade of recommendation 2013: 1C

Autologous cell salvage may be used in obstetrics and during delivery by cesarian section, provided rhesus-immunization is avoided (postoperative rhesus prophylaxis) and a leukocyte depletion filter (40 µm) is used.

(ESA grade of recommendation 2013: 2B)

Autologous cell salvage is cost-efficient in cardiac surgery and major orthopedic surgery.

ESA grade of recommendation 2013: A

Approval: 5 LS + 4 IWG

Abstention: 5 LS

In the Austrian Structural Healthcare Plan (ÖSG 2012), the availability of autologous cell salvage methods in hospitals providing specialized and centralized medical services has been defined as an infrastructure requirement.

13. The irradiation of wound blood contaminated by cancer cells could promote the acceptance and use of autotransfusion in cancer surgery (NICE Guideline; 18). The proliferation of radiosensitive cancer cells must be prevented by gamma radiation (50 Gy). Irradiation assumes the availability of an irradiator authorized according to the Medicines Act.

Approval: 8 LS + 4 IWG

Abstention: 2 LS

14. Reinfusion of unwashed wound blood is not recommended.

Approval: 9 LS + 4 IWG

Abstention: 1 LS

<u>Clinical question:</u> Can hemorrhagic anemia be influenced by blood withdrawal for diagnostic purposes?

15. The relevance of blood loss, secondary to blood withdrawal for diagnostic purposes, during and after surgery is considered little in adults (exception: intensive care setting, long-term treatment). Nevertheless, these losses should be reduced to a reasonable minimum and sample volumes should be kept as small as possible, while still bearing in mind the technical demands of the laboratory devices and the analytical methods used.

Approval: 9 LS + 4 IWG

Abstention: 1 LS

Individualized measures to minimize intra- and postoperative hemorrhage

During procedures with a risk of bleeding and in patients with specific clotting disorders, individualized procoagulatory measures are additional to the general steps taken to stop coagulopathic intra- and postoperative hemorrhage (13). Targeted management of coagulopathy requires rapid availability of laboratory tests, which can sensitively show the pathophysiologically relevant clotting disorders. These include, amongst others, hyperfibrinolysis, combined clotting factor deficiencies secondary to loss, consumption, dilution, disorders of thrombin generation and fibrin polymerization, and disorders of platelet function (13). Where appropriate, it may be necessary to consider the effects of previous anticoagulation therapy, antiplatelet therapy and pre-existing clotting disorders. These complex pathomechanisms of severe intra- and postoperative hemorrhage may occur in combination and change dynamically during the surgical procedure.

Laboratory-based treatment algorithms involve the identification of the clotting disorder, its therapeutic correction and subsequent monitoring of effectiveness. Treatment according to algorithms is an established practice in acute medicine (e.g. for resuscitation). Treatment according to algorithms has also proven itself in the acute situation of severe intraoperative hemorrhage (13).

16. In cases of intra- and postoperative hemorrhage, individualized therapeutic interventions to promote clotting should be applied according to (the hospital's own) treatment algorithms.

ESA grade of recommendation 2013: 1B

Approval: 8 LS + 4 IWG

Abstention: 2 LS

<u>Clinical question:</u> Which laboratory tests (PTZ, aPTT, platelet count, fibrinogen [Clauss assay], further stepwise diagnostic schemes, F XIII, vWF Ag, platelet function, etc.) are required for severe intraoperative hemorrhage? Which target levels should be aimed at?

In the general intra- and postoperative setting of severe hemorrhage, routine clotting tests are of secondary importance for deriving any therapeutic consequences. However, in specific clinical situations, global coagulation testing does play a decisive role, for example, in the management of patients with pre-existing anticoagulation and those with congenital coagulopathy.

17. In cases of severe hemorrhage, the repeated request for PTZ, aPTT, TZ, platelet count and reptilase time/bathroxobin time is recommended in specific treatment cases, especially in cases of pre-existing anticoagulation and pre-existing coagulopathy. Due to the delayed availability of laboratory results, blind coagulation therapy should be considered in cases of severe hemorrhage, even before receiving the final laboratory results, while still taking the typical pathomechanisms of hemorrhage for the particular procedure into account.

In principle, target values at the lower end of the normal range should be aimed at using procoagulant therapy.

Approval: 9 LS + 4 IWG

Abstention: 1 LS

Determination of fibrinogen levels (using the Clauss assay) is recommended for perioperative hemorrhage.

Target value: > 1.5 - 2 g/L

ESA grade of recommendation 2013: 1C

Approval: 8 LS + 4 IWG

Abstention: 2 LS

Low fibrinogen levels and thrombocyte aggregation correlate with the bleeding rate (13). Platelet function tests may be pathological, however, purely as a result of surrounding conditions and specific theatre situations (e.g. during use of the heart-lung machine). Optimization of platelet function could become important in the management of hemorrhage in specific treatment situations (e.g. on-going antiplatelet therapy in cases of coronary stent insertion).

A Cochrane analysis (19) and subsequent published prospective randomized clinical studies indicate that standardized management employing available point-of-care laboratory tests, i.e. ROTEM and TEG, with pre-defined trigger values for therapeutic intervention can improve outcome, especially in cardiovascular surgery, visceral surgery and major orthopedic surgery (13). Furthermore, reduction of allogeneic blood transfusions, improvement of patient outcome (revision rate for hemorrhage, massive transfusion, thromboembolic events, mortality) and reduction of transfusion-associated costs have been demonstrated after using a treatment algorithm based on ROTEM in comparison with one based on routine clotting tests (20). Early detection of pathomechanisms of acquired coagulopathy (e.g. hyperfibrinolysis, fibrin polymerization disorder) and their timely optimal correction are considered to be the reason for the improved outcome from a patient perspective and from a health economics perspective.

In the Austrian Structural Healthcare Plan (ÖSG 2012), the availability of point-of-care diagnostic coagulation tests in hospitals providing specialized and centralized medical services has been defined as an infrastructure requirement.

18. In the light of recent data, if a ROTEM is available, a practicable ROTEM-based algorithm may be used for established hemorrhage to clarify the cause of perioperative coagulopathy, especially in cardiovascular surgery, visceral surgery and major orthopedic surgery.

Approval: 8 LS + 4 IWG

Abstention: 2 LS

<u>Clinical question:</u> Which procoagulatory measures should be recommended for the targeted management of coagulopathy?

In terms of POBM, the inappropriate transfusion of all allogeneic blood products, including platelet concentrates and fresh frozen plasma (FFP) should be avoided. The efficacy of FFP in correcting an acquired coagulopathy secondary to perioperative hemorrhage is very low (21), yet does carry relevant risks, e.g. pulmonary failure (transfusion-related acute lung injury [TRALI]), volume overload (transfusion-associated circulatory overload [TACO]), immunomodulation (transfusion-associated immunomodulation [TRIM]), infections, multiple organ failure.

19. The targeted use of substances to promote coagulation, orientated on the patient's current clotting profile, is recommended.
The targeted use of coagulation-promoting substances (e.g. antifibrinolytic agents, individual clotting factor concentrates, clotting factor concentrates in combination, desmopressin, protamine, recombinant factor VIIa) is recommended in conjunction with the monodisciplinary anesthesiological recommendations of the ESA guideline 2013 (Chapter 7) (13).
The avoidance of inappropriate transfusion of FFP is recommended.
Approval: 8 LS + 4 IWG
Abstention: 2 LS

FFP, or Octaplas, has an indication e.g. in cases of factor V deficiency, factor XI deficiency, plasma exchange, massive transfusion (> 150 mL/min in 20 minutes, > 50 % loss of blood volume in three hours) (22). An inappropriate transfusion is also considered to be, amongst others, a too small dose in cases of coagulopathic hemorrhage.

Clinical question: Which graduated plan should be used for the management of conditions refractory to platelet transfusion?

Refractoriness to platelet transfusion is the failure to achieve a rise in the level of blood platelets following the transfusion of fresh compatible platelet concentrates. The cause of refractoriness may be either immune or non-immune based, with the non-immune causes being more common (e.g. peripheral consumption in cases of diffuse hemorrhagic or septic patients). Immune-related refractoriness is due to anti-platelet antibodies, with HLA class I antibodies the primary cause. In up to 30 % of cases, HLA antibodies are also associated with HPA antibodies. These constellations can lead to supply problems for the patient.

20. In a known condition refractory to platelets or with failure to achieve a rise in the level of blood platelets after the administration of two (fresh) platelet concentrates, we recommend proceeding according to the graduated plan in the German Medical Association's "Cross-Sectional Guidelines for Therapy with Blood Components and Plasma Derivatives", 4th edition (22).
Approval: 9 LS + 4 IWG
Abstention: 1 LS

Clinical question: How should the actual blood loss be measured in daily clinical practice?

The actual external blood loss is usually estimated incorrectly in comparison with the exact measurement of blood volumes in drapes, on the floor and in the suction device. The exact quantification (e.g. by means of weighing drapes) is time consuming, however, and the reaction of the individual patient's coagulation system to blood loss varies. Internal blood loss is only recognizable from the clinical picture or on imagery.

21. Roughly estimated increased blood loss (e.g. in drapes, suction device) or suspected internal hemorrhage should prompt further investigations (e.g. full blood count, clotting tests, imagery).

Approval: 7 LS + 4 IWG

Abstention: 3 LS

3. Measures prior to and during hemorrhagic anemia toincrease the tolerance of anemia

Physiological tolerance of anemia comprises compensatory mechanisms to maintain tissue oxygen supply during anemia. Despite the presence of hemorrhagic anemia, the extent of regional or global ischemia can be delayed by reduction of oxygen consumption and/or increasing oxygen delivery or extraction. If hemoglobin levels fall below the critical lower threshold, then in the absence of therapeutic intervention organ damage or death of the patient will occur.

Clinical question: Which parameters can be used as a sign that transfusion is indicated? Which measures should be taken to bring these parameters into the normal range prior to transfusion?

Hypovolemia, as well as anemia, can lead to hypoperfusion and organ ischemia with similar metabolic changes, such as a rise in lactate, increased base excess, decreased gastric pH, and clinical signs (physiological transfusion triggers), such as renal impairment (23), cold or mottled skin, tachycardia, ST segment alterations and arrhythmia. Hemodynamic parameters for measuring microcirculation and current tissue oxygenation in the critical organs are at present not yet available for routine use; measured and calculated macrocirculation parameters (e.g. mixed venous oxygen saturation, oxygen delivery and consumption) do not allow conclusions to be drawn about the regional oxygen supply. Hypovolemia is more easily detected by monitoring cardiac preload than by measuring conventional pressure parameters (e.g. arterial blood pressure, central venous pressure) (13).

22. If there are any signs of decreased organ perfusion (the course of metabolic or hemodynamic parameters), then normovolemia should be restored, the current hemoglobin level measured and physiological transfusion triggers assessed.

Approval: 10 LS + 4 IWG

Clinical question: Which measures increase physiological tolerance of anemia?

Oxygen supply can be affected by increasing cardiac output and oxygenation. Oxygen consumption can be affected, for example, by eliminating stressors and by therapeutic hypothermia.

23. The following anesthesiological intensive-care measures in particular may be considered to increase tolerance of anemia in an individualized manner appropriate to the situation:
Increase oxygen supply by optimizing the stroke index (including the use of volume replacement therapy, vasopressors, inotropes, vasodilators) and optimization of ventilation (hyperoxic, normocapnic).

Reduce oxygen consumption by means of therapeutic (mild) hypothermia, adequate muscle relaxation, elimination of stressors (by achieving adequate depth of sedation and anesthesia and providing analgesia).
Avoid or treat severe disorders, such as sepsis, trauma, cardiac disease.
Avoid drug interactions, which promote anemia or bleeding.
Approval: 10 LS + 4 IWG

According to the perioperative treatment pathway, on leaving the area of intensive monitoring (theatre, recovery ward, intensive-monitoring unit, intensive care ward) treatment of anemic patients, secondary to hemorrhage, is continued on the regular ward where the possibilities of monitoring and measures to increase tolerance of anemia are reduced.

24. The following measures in particular may be considered to increase tolerance of anemia on the regular ward following surgery:
Maintenance of normovolemia; pain management; continued treatment of pre-existing, and avoidance of secondary, disorders; avoidance of those drug interactions which promote anemia or bleeding; consider passive, instead of active, mobilization; oxygen insufflation.
Postoperative correction of iron deficiency may be considered, but it must be expected that the therapeutic effect is delayed.
Approval: 10 LS + 4 IWG

The compensation mechanisms described above for anemia are decisive for the extent of a patient's tolerance of anemia. They are also detectable in patients under long-term therapy with beta-receptor blockers, as well as in infants, children, elderly patients and patients with pre-existing cardiac disorders.

Clinical question: Should the tolerable blood loss be calculated?
Blood volume, circulating red blood cell volume and the critical threshold of tolerable blood loss may be calculated to increase vigilance and risk assessment of relevant hemorrhagic anemia (24,25).

25. It is recommended to calculate tolerable blood loss before induction of anesthesia, particularly in high-risk patients (see formula in the attachment).
Exceeding the threshold value on its own is not recommended as a trigger for a transfusion of RCCs, but rather as a trigger to measure the current hemoglobin level and to look for clinical or metabolical signs of decreased organ perfusion, while taking the clotting situation into account.
Approval: 10 LS + 4 IWG

4. Measure for hemorrhagic anemia: Transfusion of RCCs

Clinical question: Which hemoglobin levels are regarded as a transfusion trigger for which patients during which operations?

Hemoglobin levels, measured by full blood count analysis or, if not available in time, by blood gas analysis, should be used to estimate whether hemorrhagic anemia requires blood transfusion.

Due to the unpredictable nature of the dynamics of hemorrhagic anemia, a higher transfusion trigger appears appropriate in cases of hemorrhage, or in procedures or following the surgery phase with a risk of bleeding, compared with non-bleeding patients.

26. In cases of hemorrhage, a hemoglobin level of 7-9 g/dL is recommended as an upper laboratory transfusion threshold.

ESA grade of recommendation 2013: 1C

Approval: 10 LS + 4 IWG

With hemoglobin levels above 9 g/dL, RCCs should only be administered if clinical signs of global or regional oxygen deficit are present, especially after taking relevant previous disorders into account (e.g. ST segmental changes in patients with coronary heart disease, obstructive pulmonary disease, after previous pneumonectomy).

Approval: 10 LS + 4 IWG

Coagulopathy alone is not an indication for transfusion of RCCs.

After stopping the bleeding, after the surgery phase with a risk of bleeding or after the operation, low hemoglobin levels may be tolerated, provided there is normovolemia and no clinical or metabolic signs of decreased organ perfusion.

So-called restrictive transfusion thresholds ≤ 9 g/dL (as opposed to liberal transfusion thresholds > 9 g/dL) had no adverse effect on patient outcome, including rehabilitation (6,26,27), but they did reduce transfusion rates and costs. Such individualized patient management assumes knowledge by all health care professionals involved and continuous monitoring of the patients during the entire treatment pathway, including on the regular ward.

Hemoglobin levels as transfusion triggers should not be assessed on their own; individual ability to compensate and the risk factors of the affected patient should be used as so-called physiological transfusion triggers (e.g. ECG changes).

Only so many RCCs should be administered until the appropriate threshold values have been reached. In adults, the number of RCCs required can be estimated from an expected rise in hemoglobin levels of 1 g/dL per RCC. Unnecessary transfusions which exceed the threshold level can be avoided by following up the hemoglobin value approximately one hour after transfusion. The single administration of one RCC may also be sufficient.

27. After bleeding has been stopped and following the surgery phase with a risk of bleeding, a hemoglobin level of 6-8 g/dL should be used as a transfusion trigger with ongoing monitoring of clinical and laboratory parameters (modified according to 22).

Approval: 10 LS + 4 IWG

With hemoglobin levels above 8 g/dL, RCCs should only be administered if there are clinical signs of global or regional oxygen deficit, especially after taking relevant previous disorders into account (22).

Approval: 10 LS + 4 IWG

Recommendations for the transfusion of red blood cells in cases of acute anemia take into account the current hemoglobin level, the physiological ability to compensate the low level of oxygen in the blood (ability to compensate), the presence of cardiovascular risk factors (risk factors) and clinical signs of anemic hypoxia (physiological transfusion triggers). From the Cross-Sectional Guidelines (German Medical Association) for Therapy with Blood Components and Plasma Derivatives. Published by the Executive Board of the German Medical Association upon the recommendation of the scientific advisory council (2008) (22).

Hemoglobin range in g/dL	Ability to compensate/risk	Transfusion of RCCs
≤ 6		**YES***
6-8	**Compensation adequate No risk factors**	**NO**
	Compensation limited Risk factors present e.g. CHD, heart failure, cerebrovascular insufficiency	**YES**
	Signs of anemic hypoxia: tachycardia, hypotension, ECG, ischemia, lactic acidosis	**YES**
8-10	**Signs of anemic hypoxia: tachycardia, hypotension, ECG, ischemia, lactic acidosis**	**YES**
> 10		**NO****

*** In individual cases, lower Hb levels may be tolerated without transfusion if there is adequate compensation and no risk factors.**

** In individual cases, transfusion to Hb levels > 10 g/dL may be indicated.

PLEASE NOTE: Hb levels alone are no adequate measure for oxygen supply

In cases of hypovolemia, the hematocrit does not correctly reflect the actual red blood cell deficit. Individual factors should be taken into account!

Fig. 2. Indications for transfusion according to hemoglobin levels and physiological transfusion triggers (ability to compensate, risk factors)

Clinical question: Which preparatory measures (e.g. irradiation) should be employed for which indication? Are there any references to national/international recommendations?

RCCs are produced from voluntary donors, either from freshly acquired whole blood or mechanically using cell separators. The standard preparation in the German-speaking countries is leukocyte-depleted RCC in additive solution. The risk of exposureto leukocyte antigens (above all HLA antigens) and of febrile non-hemolytic transfusion reactions is reduced by leukocyte depletion, and the transmission of cell-bound viruses (e.g. CMV) is largely prevented. Immmunomodulatory effects should also be less frequent. The additive solution replaces the plasma and serves above all as a nutrient solution for the red blood cells. Key data regarding leukocyte-depleted RCC are: volume (including additive solution) approximately 300 mL, hematocrit between 50 and 70 %, leukocyte content < $1*10^6$, shelf life up to 49 days, depending on the type of additive solution.

RCCs can be further processed for certain indications. For example, washed RCCs are available and are indicated especially in patients who respond to plasma protein with severe allergic reactions. Washed RCCs must be transfused as rapidly as possible.

Irradiation of RCCs is performed using a mean dose of 30 Gy and is indicated in immunosuppressed patients to prevent the usually lethal transfusion-associated graft-versus-host disease (TA-GvHD) (Cross-Sectional Guidelines of the German Medical Association 2008) (22).

Clinical question: Can "type and screen" be recommended instead of the serological test for tolerability?

The screening examination for serological compatibility of donors and recipients can be undertaken either by "type and screen" and/or by serological compatibility testing. So-called "type and screen" is carried out in Scandinavian countries, the United Kingdom and Switzerland. Typing involves determining the ABO and Rh status; the sample is then screened using an antibody detection test to detect anti-erythrocyte antibodies. Matching the data is done by a fully validated electronic system, for which reason "type and screen" is also often referred to as electronic crossmatching. In the presence of antibodies or in cases of previously confirmed positive antibody results, however, serological compatibility testing should always follow. The advantages of "type and screen" are the more rapid availability of matching blood products and the simpler logistics; disadvantages are dependency on individual case history, high software validation costs and a residual risk that rare antibody/antigen constellations are not detected. In Austria and Germany, pretransfusional screening is specified by relevant guidelines. These contain information on the ABO and Rh typing procedure, how to perform the antibody detection test, and serological compatibility testing (crossmatching).

Clinical question: When can the antibody detection test be dispensed with?

Blood group typing always includes an antibody detection test to discover any irregular blood group antibodies of the patient – there is international consensus on this. If the blood group is already known, then a further antibody detection test may be dispensed with if the last screening test result is no older than seven days and there is proof that no known immunization triggers (pregnancy, abortion, transplantation, transfusion) have taken place in the previous three months. The compatibility sample must not have been taken more than 72 hours prior to the planned transfusion. Only in emergency cases is it possible to deviate from this approach, although this does not absolve from the obligation of following up the tests.

Clinical question: What do clinicians have to observe during transfusion (medicolegal issues)?

Before a planned surgical procedure with a transfusion probability of more than 10 %, patients must be fully informed by the attending doctor about effects and adverse reactions of blood components and about possible alternatives, such as anemia management (preoperative autologous blood donation, amongst others) (22). An appropriate consent form, including the patient's declaration of informed consent for transfusion, should be available in the department.

28. We recommend the use of standardized informed consent forms for elective procedures with a transfusion probability of > 10% to document that the duty to obtain informed consent has been fulfilled.
Approval: 10 LS + 4 IWG

Blood components are subject to the Medicines Act. The blood product request is therefore a prescription and must bear a doctor's signature.

29. We recommend training and applying the hospital's own guidelines on the use of blood components.
Approval: 10 LS + 4 IWG

Clinical question: When should preoperative autologous blood donation be recommended? How can anemization be avoided?

If, in cases of planned surgical procedures and given a regular course of the operation, there is a transfusion probability of at least 10 % from the hospital's own experience, then the patient should be fully informed individually and in good time about the risks of allogeneic blood transfusion, the possibility of using autologous blood, and the benefits and risks of autologous blood donation and use. The main advantage of preoperative autologous blood donation is the net gain of red blood cells (donated stored red blood cells plus regenerated cells). This only applies, however, if there is adequate time between the donation and surgery. The most important points in favor of preoperative autologous blood donation are:

- immunological compatibility (no TRIM / is also possible in cancer patients), generally no infection risk (including currently unknown, new or undetectable dangerous pathogens); acute signs of inflammation can be recognized when taking the patient's history or during screening
- no antibody production against red blood cell antigens

- use in patients with complicated antibody situations
- somewhat greater effect of saving allogeneic blood than with autologous cell salvage
- elimination of the compatibility test and consequently less laboratory work

What works against autologous blood donation:

- only possible in procedures planned well in advance
- increased planning effort and logistics as compared with allogeneic donation
- only possible in a few hospitals in Austria as it is regarded as pharmaceutical manufacturing and is therefore subject to permit from the Austrian Agency for Health and Food Safety (AGES) (conventional blood transfusion centers tend to be used for allogeneic donors)
- anemization due to too aggressive collection or too short an interval before the day of surgery
- risks to the donor (e.g. hematoma, collapse)
- higher discard rate, given that autologous blood donations must not be given to allogeneic blood recipients, whereas unused allogeneic blood products may be made available to another recipient; it is therefore necessary to make the indication carefully and only where there is a predictable higher transfusion rate per procedure (such as spinal surgery, revision total large joint replacements)
- the effects on the red blood cells of storage are identical to those for allogeneic blood
- likelihood of confusing RCCs
- alternative methods available (e.g. autologous cell salvage, normovolemic hemodilution)

30. We recommend preoperative autologous blood donation in procedures involving special groups of patients (e.g. rare blood types, special antibody constellation) or at the express wish of the patient if there is a high transfusion probability.

Approval: 8 LS + 4 IWG

Clinical question: How can anemization be avoided by preoperative autologous blood donation?

Preoperative autologous blood donation requires precise planning. Early contact with the patient allows individual planning (depending on the indication for surgery, ability of the bone marrow to produce red blood cells and associated disorders and concomitant medication) and attention to baseline hemoglobin levels allowing autologous blood to be taken in order to avoid anemia or to allow alternative methods to be considered. An adequate amount of time between the last autologous blood donation and the date of surgery is essential. Here, intensified autologous blood collection of several RCCs in the first two weeks of the autologous collection schedule and a two- to three-week interval before surgery appear to achieve the greatest net gain. Erythropoietin (EPO) and iron administration should be considered in cases of inadequate regeneration of blood levels. This too requires a certain lead time as red blood cell maturation is increased but not accelerated.

31. In cases of preoperative autologous blood donation, we recommend a minimum interval between the last donation and the date of surgery of two weeks.

Should preoperative anemia be provoked by the autologous blood donation, then it should be followed up proactively and any insufficient regeneration of blood promptly corrected by the administration of iron and/or EPO.

Since in cases of low normal ferritin levels (< 100 µg/L), even the withdrawal of 1 - 2 RCCs leads to a critical reduction of iron stores, the indication for iron prophylaxis should be readily made.

Approval: 10 LS + 4 IWG

Clinical question: How can the transfusion probability be predicted? To what extent (according to public service obligations) should allogeneic blood be made available in our hospitals for particular operations?

32. We recommend a procedure-specific data capture at least once a year of the transfused patients in relation to the total number of operated patients. With a transfusion probability of ≥ 10 %, at least the average number of allogeneic blood products required for each procedure during the observation period should be made available (each hospital's individual blood request list).

Approval: 9 LS + 4 IWG

Abstention: 1 LS

Clinical question: How can the provision of blood products be optimally timed?

The first blood group typing (within the catchment area of the respective Information Network/Association of Hospitals) including an antibody detection test can already be carried out approximately six weeks before the planned date of surgery. Antibody detection test and serological compatibility testing must then be repeated 72 hours before surgery at the earliest. If no known immunization triggers have occurred in the previous three months, then this period may be extended to seven days prior to surgery. With this approach, there is usually enough time in the majority of cases for antibody screening, dates for any necessary preoperative autologous blood collections can be set, and provision of the required blood products on the day of surgery is unproblematic.

In order to avoid repeat examinations, blood group typing and antibody detection test need not be undertaken until 72 hours prior to surgery; it must be taken into account that if irregular anti-erythrocyte antibodies (< 5 %) are detected, then surgery dates may be postponed, due amongst others to the need to find compatible products or the necessity for autologous blood donations.

33. We recommend the provision of blood products (depending on the hospital's own blood requirement specification) within 72 hours of surgery.

For logistic reasons, initial blood group typing and antibody detection testing may be done at least six weeks before the date of an operation with a risk of bleeding (during the preoperative investigational workup).

Approval: 10 LS + 4 IWG

Clinical question: Which ratio between provision of blood products and actual transfusion should be aimed at for a smooth supply?

34. We recommend a ratio of < 2:1 (ideal target 1.7) between available and transfusable allogeneic blood products for elective procedures.
Approval: 10 LS + 4 IWG

Clinical question: Which standard key data could we prospectively gather nationwide to document the intended harmonization of the use of RCCs?

35. The following key data could be used prospectively nationwide to document the target improvement goal (provided the technical prerequisites are available):
Number of blood components received by the blood bank per year
Number of blood components made available per year and surgical procedure
Number of transfused blood components per year and surgical procedure
Ratio of blood components made available / transfused per year and department
Ratio of blood components made available / transfused per year and surgical procedure
Number and percentage of discarded blood components per year
Indication-related transfusion triggers
Approval: 9 LS + 4 IWG
Abstention: 1 LS

The above and other key data are to be found in a proposal by the working group TS064 of the European Committee on Blood Transfusion (CD-P-TS) of the European Directorate for the Quality of Medicines and Health Care (EDQM) of the Council of Europe. (28)

5. Methods of allocation and implementation

Clinical question: How can recommended actions be disseminated?

36. The LS involved in the perioperative treatment pathway should convey the medical contents of the present recommended actions to colleagues via the teaching curricula of the specialties and continuous professional development activities.
Approval: 9 LS + 4 IWG
Abstention: 1 LS

The development of auxiliary tools could alleviate implementation in daily clinical practice (e.g. a safety checklist for operations with a risk of bleeding as a modification of the WHO Safety Checklist) (Fig. 3).

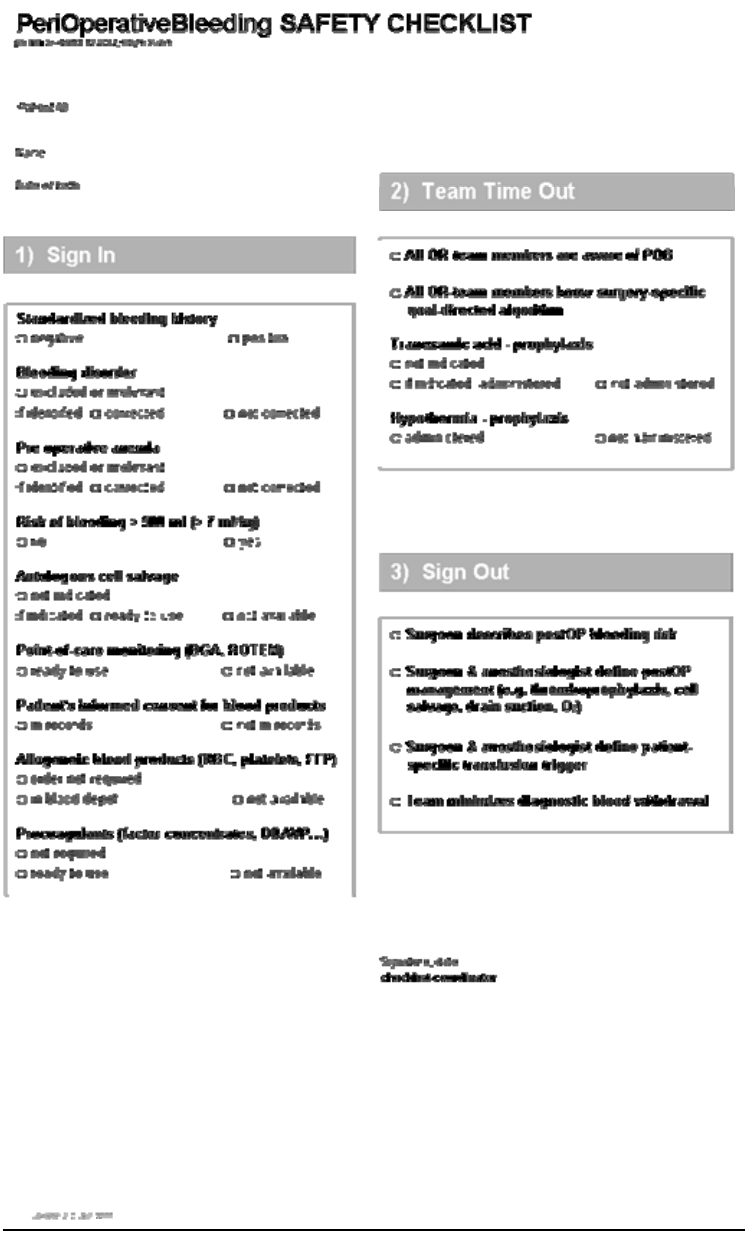

Fig. 3. Draft of a surgical safety check-list for POBM

37. Information and material for informed consent expressed in a manner which is understandable for lay people can promote the understanding of patients and relatives for the package of measures in the anemia management program (POBM) and so increase compliance for the additional time required, especially for the correction of preoperative anemia. Approval: 10 LS + 4 IWG

Clinical question: How can recommended actions be implemented promptly and sustainably?

Continual documentation of results and outcome data, including continual benchmarking, was the critical success factor for the implementation of POBM and for achieving the improved patient outcome and

reduction of costs (11, 30). As part of the healthcare reform 2013, results, processes, structures and finances within the health system are to be documented and made transparent. It may be assumed that nationwide endeavors are underway (apart from the present recommended actions) to record these quality indicators uniformly and automatically.

The integration of the present interdisciplinary, interprofessional recommended action as medical source guidelines of a future Federal Quality Guideline for POBM can make their rapid and sustainable implementation possible.

Attachment

Formulae for calculating tolerable blood loss (TBL) (in core statement 25):

TBL (mL) = blood volume (mL) x (preoperative hematocrit (L/L) – tolerable hematocrit (L/L) x 0.91

Blood volume (females, L) = 0.3561 x height (m) + 0.03308 x weight (kg) + 0.1833

Blood volume (males, L) = 0.3669 x height (m) + 0.03219 x weight (kg) + 0.6041

Conversion of hematocrit from % to L/L: divide by 100

Conversion from hemoglobin (Hb) to hematocrit (Hct): Hb = Hct x mean corpuscular hemoglobin concentration MCHC (g/dL)

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