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Review Article

Pre-operative haematological assessment in patients scheduled for major surgery

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Summary

Peri-operative anaemia, blood loss and allogeneic blood transfusion are associated with increased postoperative morbidity and mortality, and prolonged hospital stay. A multidisciplinary, multimodal, individualised strategy, collectively termed 'patient blood management', may reduce or eliminate allogeneic blood transfusion and improve outcomes. This approach has three objectives: the detection and treatment of peri-operative anaemia; the reduction of peri-operative bleeding and coagulopathy; and harnessing and optimising the physiological tolerance of anaemia. This review focuses on the pre-operative evaluation of erythropoiesis, coagulation status and platelet function. Where possible, evidence is graded systematically and recommended therapies follow recently published consensus guidance.

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Introduction

A significant proportion (30–35%) of allogeneic blood is transfused for acute postoperative anaemia. The proportion of patients transfused after a given operation varies substantially between hospitals [1–3].

The expense and harm associated with blood transfusions have prompted a growing interest in multidisciplinary, multimodal, individualised strategies, collectively termed 'patient blood management': this aims to reduce the number of blood transfusions and to improve patient outcomes [4]. The 63rd World Health Assembly endorsed this approach in its resolution 'Availability, safety and quality of blood products' [5].

Patient blood management has three objectives: the detection and treatment of peri-operative anaemia; the reduction of peri-operative bleeding and coagulopathy; and harnessing the physiological tolerance to anaemia. This review focuses on the first two of these three objectives, by grading evidence systematically where possible and recommending therapies in accordance with recently published consensus guidance [6–12].

Pre-operative anaemia

Pre-operative anaemia is, unsurprisingly, independently associated with subsequent transfusion, but also with postoperative morbidity and mortality [13–15]. Anaemia should be detected before surgery that is likely to cause significant blood loss, preferably at least 30 days before scheduled operations (Grade 1C) [7, 8].

The World Health Organization defines anaemia for men and women by haemoglobin concentrations

less than 130 $g.l^{-1}$ and 120 $g.l^{-1}$, respectively, at sea level. A target haemoglobin concentration of at least 130 $g.l^{-1}$ should be used for all adult patients until research determines more useful 'suboptimal' pre-operative haemoglobin concentrations [12].

The cause of pre-operative anaemia should be identified and treated if possible (Grade 1C) [7, 8]. Bleeding from the upper and lower gastrointestinal tract and the genital-urinary system should be considered and investigated. The patient should be screened for coeliac disease and *Helicobacter pylori* colonisation. Major surgery may have to be rescheduled, whereas minor procedures, without blood loss, can proceed in parallel with the evaluation of anaemia [1, 6–9].

There are three types of iron-restricted erythropoiesis, the most common cause of anaemia worldwide: absolute iron deficiency; iron sequestration due to inflammation; and functional iron deficiency due to insufficient erythropoiesis-stimulating agents. Serum ferritin concentrations less than 30 $\mu g.l^{-1}$ indicate absent iron stores i.e. iron deficiency anaemia, treatable with oral iron [16]. Serum ferritin concentrations 30–100 $\mu g.l^{-1}$ suggest a combination of iron deficiency anaemia and anaemia of chronic disease, which is treatable with intravenous iron [17]. Serum ferritin concentrations more than 100 $\mu g.l^{-1}$ suggest anaemia of chronic disease due to iron sequestration. Transferrin saturation measures iron transport capacity, not the amount of stored iron. Values less than 20% indicate anaemia that will respond to a combination of parenteral iron and erythropoiesis-stimulating agents [16, 17]. Iron sequestration is identified by more than 5% red cells being hypochromic or a reticulocyte haemoglobin content less than 27 pg [17]. If these measures are unavailable, the concentration of soluble transferrin receptor, with or without the ferritin assay, may help determine whether anaemia of chronic disease is contributed to by iron deficiency [16, 17]. Normal red cell volumes (80–100 fl) does not exclude iron deficiency anaemia, for instance when there is coexisting vitamin B_{12} or folate deficiency, postbleeding reticulocytosis, during oral iron treatment, with alcohol intake or mild myelodysplasia. The variation in the volumes of red cells, the 'red cell distribution width', can help differentiate iron deficiency from other microcytic anaemias, for instance thalassaemia. The advantages, disadvantages and diagnostic value of these variables are summarised in Table 1.

When iron-restricted erythropoiesis does not explain anaemia, other investigations including serum B_{12} (especially for those older than 60 years), lactate dehydrogenase and serum creatinine, may help exclude other nutritional deficiencies, haemolysis or renal disease. Red cell folate may be useful if malabsorption or severe malnutrition is present [16, 18]. Patients should be referred to a haematologist for further evaluation when a diagnosis is not reached.

Management of pre-operative anaemia

Normal erythropoiesis needs a healthy bone marrow with an adequate supply of various nutrients (iron, vitamins C, B_1, B_6, B_{12} and folic acid), and hormones (erythropoietin, thyroid hormones and steroids). The possible benefits of oral and intravenous iron, with or without erythropoiesis-stimulating agents, are discussed below. Pre-operative transfusion should be restricted to patients who are bleeding with severe anaemia or poor physiological reserve.

Patients deficient in vitamin B_{12} should be given 1 mg vitamin B_{12} (intramuscularly or subcutaneously) and 5 $mg.day^{-1}$ oral folic acid should be given to correct its deficiency [18].

Iron therapy

Iron deficiency should be treated with pre-operative oral iron whenever there is enough time and there are no contraindications (Grade 2B) [10]. In some studies, ferrous salts at doses of 100–200 $mg.day^{-1}$ for 2–4 weeks increased haemoglobin concentration, reduced transfusion rates and, in some cases, the length of hospital stay [19–22], but not in other studies [23, 24]. Postoperative oral iron is not recommended as it does not accelerate the correction of anaemia or reduce the transfusion rate (Grade −1B) [10, 24–27].

Patients without anaemia but with low ferritin levels may also benefit from pre-operative iron administration, particularly when substantial bleeding is anticipated, as they may not have enough stored iron to support rapid erythropoiesis and other metabolic requirements [7].

Intravenous iron, 3–4 weeks before surgery, should be considered: if oral iron is poorly absorbed or poorly

Table 1 Variables in iron deficiency.

Variable	Value		Advantages	Disadvantages	Diagnostic value for iron deficiency
	Normal	Iron deficiency			
Red cell volume; fl	80–100	< 80	Inexpensive, common	Decreased by chronic disease, thalassaemia and sideroblastic anaemia Affected after 24-h sample storage	Sensitive for established deficiency Useful for treatment monitoring
Red cell haemoglobin; pg	27–35	< 28	Inexpensive, common	Decreased by chronic disease, thalassaemia and sideroblastic anaemia	Sensitive for established deficiency Useful for treatment monitoring
Red cell distribution width	11–15%	> 15%	Inexpensive, common	Increased by reticulocytosis, e.g. after blood loss and treated iron deficiency	Sensitive for early deficiency Helps differentiate from other microcytic anaemias (e.g. thalassaemia)
Platelet count; $\times 10^9.l^{-1}$	140–450	> 450	Inexpensive, common	Increased after infections, trauma, allergic reactions, splenectomy, cancer and some haematological diseases	Highly suggestive of iron deficiency with microcytic red blood cells
Hypochromic red cells Low density haemoglobin	< 5%	≥ 6%	Sensitive to rapid changes in iron availability	Affected after 24-h sample storage Limited to flow cytometric analysers	Well-established for identifying iron sequestration
Reticulocyte haemoglobin content; pg	28–35	< 28	Sensitive to rapid changes in iron availability	Affected after 24 h sample storage Falsely normal if microcytosis absent or with thalassaemia Limited to flow cytometric analysers	Well-established for identifying iron sequestration and deficiency with ESAs Values < 25 pg differentiate iron deficiency and chronic disease
Red blood cell size factor; fl	91–107	< 87.7	Sensitive to rapid changes in iron availability	Limited to flow cytometric analysers	Encouraging sensitivity and specificity for detecting iron-restricted erythropoiesis
Ferritin; $ng.ml^{-1}$	30–300	< 30	Inexpensive, common	Non-specific acute phase protein, increases with age, not associated with response to ESAs (cancer)	Iron deficiency if < 30, or < 100 with inflammation; > 500 iron overload
Transferrin saturation index	16–45%	< 16%	Inexpensive, common	Negative acute phase protein, not useful after intravenous iron	Iron deficiency if < 16, < 20 iron-restricted erythropoiesis with inflammation, > 50 iron overload
Serum transferrin receptor; $mg.l^{-1}$	< 2	> 4.5	Insensitive to inflammation	Expensive, dependent on the WHO standard, increased by erythropoiesis, e.g. haemolysis, chronic lymphocytic leukaemia	In the absence of other automated measures it may help diagnosis, with or without ferritin
Ferritin index ([transferrin receptor] / log[ferritin])	< 1	> 2	Better than either component in isolation	As for serum transferrin receptors	Iron deficiency if < 1; 2–3 iron deficiency, chronic disease or inflammation

ESAs, erythropoiesis-stimulating agents.

tolerated; for anaemia of chronic disease, with or without inflammation; and when an accelerated response is required (Grade 2B) [10, 28–31]. Shorter courses of pre-operative intravenous iron, with or without erythropoiesis-stimulating agents, may be used (Grade 2B) [7, 10, 32–36]. These recommendations are also supported by the European Medicines Agency's Committee for Medicinal Products for Human Use [37]. Guidance for preventing and treating hypersensitivity reactions to intravenous iron has been published recently [38]. Intramuscular iron administration is not recommended [10].

A recent meta-analysis of 103 trials of 19 253 participants concluded that intravenous iron therapy did not increase the rates of serious adverse events or infections when compared with oral or intramuscular iron, no iron or placebo [39]. In large observational studies, peri-operative intravenous iron did not increase rates of infection or 30-day mortality [34–36]. Newer formulations, for instance iron isomaltoside and ferric carboxymaltose, can be given quickly in single large doses of 1 g or more, which is more convenient for patients and is less expensive [12, 29, 40, 41]. However, further prospective efficacy and safety trials in various surgical settings are required to make evidenced-based conclusions.

Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents should be considered for patients with anaemia of chronic disease, after the correction of nutritional deficiencies. In Europe, erythropoiesis-stimulating agents are only indicated for pre-operative patients expected to have moderate blood loss, whose haemoglobin concentration is 100–130 $g.l^{-1}$ (Grade 1A) [10, 42–45]. However, their minimum effective dose is unknown. Off-label use of erythropoiesis-stimulating agents is suggested before cardiac surgery [32, 46–48] or gastrointestinal cancer resection [49] (Grade 2B), but it is not recommended for critically-ill patients without a prior indication (Grade −1A) [10, 50].

The treatment of anaemic chronic renal failure patients and chemotherapy patients with erythropoiesis-stimulating agents has been associated with thrombo-embolic events and death [51–53]. Erythropoiesis-stimulating agents caused deep-vein thrombosis in patients undergoing major spinal surgery without thrombo-embolic prophylaxis [54]. It is important to make a distinction between erythropoiesis-stimulating agents and intravenous iron, as the latter alone does not cause supra-physiological haemoglobin concentrations and thrombocytosis. Doses of erythropoiesis-stimulating agents should be adjusted pre-operatively with reference to an individual's target haemoglobin concentration, while ensuring adequate iron supply to the bone marrow and thromboembolic prophylaxis [10, 12].

Pre-operative evaluation of haemostasis

The aims of pre-operative coagulation testing are to detect patients with abnormal bleeding caused by coagulation disorders with a high prevalence (e.g. von Willebrand disease), rarer disorders with high clinical relevance (e.g. coagulation factor deficiency in haemophilia) and drug-induced coagulopathy (e.g. dual anti-platelet therapy and vitamin K antagonists). Traditional coagulation screening tests do not reliably identify patients more likely to bleed or clot peri-operatively [55–58].

A medical history remains the most important tool for detecting inherited or acquired bleeding disorders that increase the risk of peri-operative bleeding [59]. The European Society of Anaesthesiology strongly recommends standardised pre-operative bleeding questionnaires or structured interviews to record patient and family histories of bleeding and medications, rather than routine blood tests (Grade 1C) [11]. Standardised questionnaires discriminate between bleeding from mucosal or non-mucosal tissues and the circumstances associated with bleeding, as well as other factors, such as the anticoagulant or anti-platelet drug usage (Table 2) [60, 61]. About 11% of adults answer 'yes' to an item, which qualifies as an abnormal bleeding history [60].

A bleeding history should be sought well before elective surgery to give time for diagnoses and treatment. Pre-operative staff should confirm answers with the patient or guardian. Simple laboratory tests should be performed if a history cannot be taken from an incapacitated patient and if the information is unavailable from next-of-kin: physical examination may reveal bruising, petechial lesions or defective wound healing.

Table 2 Standardised questionnaire items to detect an increased bleeding risk.

Known coagulopathy
Unexplained epistaxis
Unexplained haematoma, petechial lesions on the torso or an unusual location
Defective wound healing
Prolonged bleeding after accidental or surgical cuts, including dental work
Abnormal requirement for blood products after previous surgery
Hypermenorrhagia requiring > 7 tampons per day, bleeding > 7 days since menarche
Medication affecting coagulation: pain killers, anti-thrombotic and anti-platelet drugs, over-the-counter drugs and dietary factors

There is little evidence to support routine pre-operative laboratory testing. Guidelines suggest laboratory investigations of haemostasis in patients with normal bleeding histories when they are scheduled for surgery with a high risk of bleeding or if there is a relevant co-morbidity [61]. Global coagulation tests were not developed to predict bleeding or to guide peri-operative coagulation management, even though most hospitals perform four tests as a 'global coagulation panel'.

The activated partial thromboplastin time (aPTT) was developed to monitor the effect of heparin, to characterise clotting factors and for haemophilia research. The aPTT is sensitive to coagulation factors 1, 2, 5, 8, 9, 11 and 12, as well as heparin, fibrinogen degradation products, inhibitors, hypothermia and hypofibrinogenaemia. Multiple factor deficiencies tend to prolong the time for a given factor concentration than single factor deficiencies. An aPTT 1.5–1.8 above the normal upper limit (> 60 s) might prompt treatment.

The prothrombin time was developed to monitor and adjust the doses of coumarins. This test is sensitive to coagulation factors 1, 2, 5, 7 and 10. The prothrombin time of a sample is calibrated against that of known certified plasma samples, which generates the standard international normalised ratio (INR). A prothrombin activity below 40% might prompt treatment.

Platelet concentrations are routinely counted by automated machines, the value of which does not reflect platelet function. A platelet concentration below $50 \times 10^9.l^{-1}$ might prompt treatment.

Fibrinogen plays a major role in routine coagulation tests such as the aPTT and the prothrombin time. Two methods are used: counting the fibrinogen molecules, for example by immunology, gravitometry or heat precipitation; and measuring clottable fibrinogen, for example by Claus's method, which is affected by heparin and fibrinogen degradation products. Excessive bleeding has been reported at fibrinogen concentrations below 50–100 $mg.dl^{-1}$ [62, 63]. Fibrinogen concentrations of 200–380 $mg.dl^{-1}$ are required for sufficient fibrin clot polymerisation [64, 65]. Low pre-operative fibrinogen levels are associated with intra-operative bleeding during cardiac surgery. The fibrinogen concentration is the single variable best correlated with postpartum bleeding [66]. Individual coagulation factors and molecular markers of the coagulation and fibrinolytic systems are rarely assayed pre-operatively, because these tests can take a long time and might be unavailable. Patients with inherited coagulation defects may exsanguinate with trauma or major surgery unless deficient factors are replaced, for instance factors 8 and 9 or von Willebrand factor concentrate.

Routine pre-operative coagulation tests are poor predictors of peri-operative bleeding and mortality. Although aPTT > 1.8 times normal and INR > 1.8 have been associated with mortality in trauma, particularly when they co-exist, moderately-prolonged times have not been associated with adverse outcome [56, 63, 67, 68]. Platelet concentration also does not independently associate with mortality in emergency medicine [69].

Global coagulation tests are inadequately standardised, with variable sensitivities of test reagents and variation between laboratories and investigators. Routine tests do not identify which coagulation factor is deficient. The speed of fibrin strand formation is assessed by the prothrombin and aPTT, but they do not assess the mechanical and functional properties of clot formation. Functional fibrin polymerisation may be impaired despite normal fibrinogen concentration, in the same way that platelet function may be impaired despite normal platelet concentration. Global coagulation tests are of plasma at a standardised temperature in the absence of platelets and blood cells. Tests of plasma function do not interrogate the

complex haemostatic interaction of plasma proteins, platelets and the vessel wall.

However, an increasing number of tests can be performed immediately on venesected whole blood, using point-of-care automated devices. The measurement of prothrombin time and aPTT times immediately before surgery can be useful for patients chronically anticoagulated, for instance using 'CoaguChek®' (Roche Diagnostics Ltd, Burgess Hill, UK). New tests are anticipated for direct factor Xa inhibitors. Immediate test results are not identical to laboratory test results, but normal values suggest that vitamin K antagonists or direct thrombin inhibitors, such as dabigatran, have been sufficiently eliminated.

Platelet function tests

The European Society of Anaesthesiology recommends assessing pre-operative platelet function only for patients with an abnormal bleeding history (Grade 2C) [11]. The widespread adoption of anti-platelet agents into everyday clinical practice has revolutionised contemporary care of cardiovascular patients. However, these drugs increase peri-operative bleeding, a problem that will become increasingly important [70–72]. Platelet function tests are first level tests in the pre-operative evaluation of patients with a positive bleeding history (Fig. 1) [60, 73]. Second-level tests are indicated when global panel and viscoelastic coagulation tests cannot diagnose the haemostatic defect responsible for bleeding, particularly for patients taking anti-platelet drugs, patients with inherited or acquired platelet defects, and patients on extracorporeal bypass circulation.

There is still no simple reliable method for measuring platelet function. Static tests, such as measurement of β-thromboglobulin, capture only one single point in time and cannot accurately reflect the dynamic processes encountered intra-operatively. Dynamic tests such as the bleeding time reflect the time-dependent contribution of platelets to overall clot formation. However, the bleeding time is poorly standardised, is dependent upon temperature, catecholamines and vascular disorders, lacks specificity and sensitivity, increases non-specifically during surgery and transfusion and does not predict bleeding [67, 74, 75].

Several modern analysers assess the platelet response to an agonist. The platelet function analyser PFA-100® (Siemens Healthcare Diagnostics, Marburg, Germany) provides a measure of platelet function in citrated whole blood at high shear rates. This

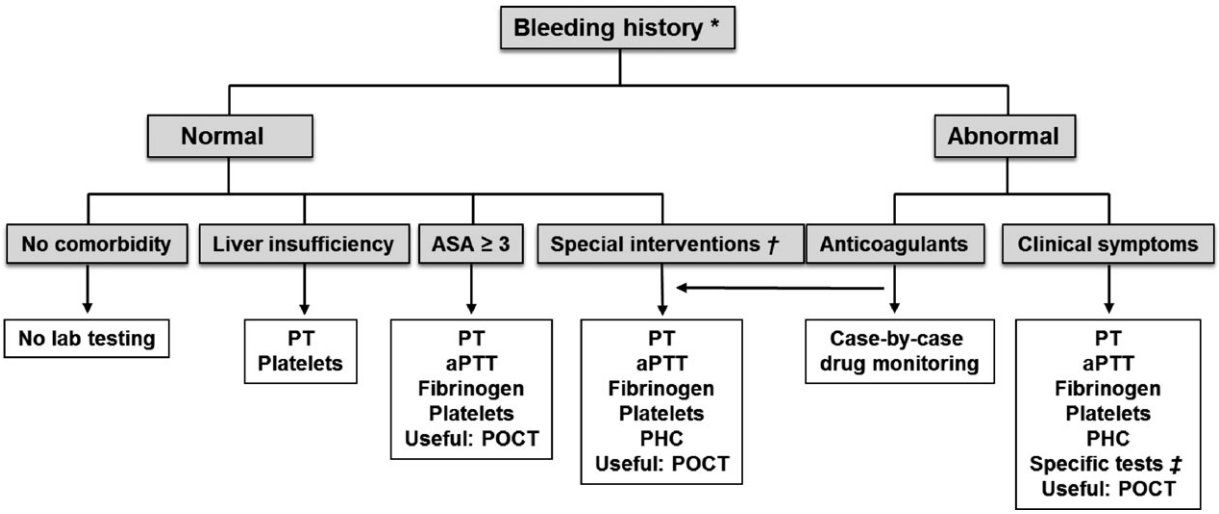

Figure 1 Austrian algorithm of the pre-operative coagulation work-up [60].
aPTT, activated partial thromboplastin time; PHC, primary haemostasis capacity; POCT, point-of-care functional coagulation monitoring (e.g. ROTEM); PT, prothrombin time. *Standardised questionnaire (Table 2). †Laboratory testing may be performed before intracranial and spinal surgery, retina surgery, neuraxial blockade with catheter insertion in non-obstetric patients, infra- or supra-clavicular approach of central venous catheter insertion. ‡In patients with known coagulopathy, e.g. factor VIII activity in haemophilia A.

instrument aspirates 800 μl of blood through a capillary and microscopic aperture within a membrane coated with platelet agonists, collagen and either adrenaline or adenosine diphosphate (ADP). Activated platelets attach to the membrane where they aggregate to form a plug. The time taken to occlude the aperture is a function of platelet concentration and reactivity, von Willebrand factor activity and haematocrit [76]. The normal times for aperture closure are less than 165 s for adrenaline cartridges and less than 186 s for ADP cartridges. The response of aperture closure time to desmopressin should be assessed in patients with platelet dysfunction, unless there are contraindications. This method can rapidly identify pre-operative platelet disorders, including those associated with von Willebrand syndrome [60, 73, 77]. In cardiac surgical patients, the pre-operative aperture time correlated with postoperative blood loss in some cardiac studies [78], but not in others [79].

Other platelet aggregometers measure changes in luminescence or impedance after platelet agonist stimulation. Originally, these techniques were only performed by specialised laboratories as their widespread adoption has been limited by several technical barriers. The 'Multiplate' aggregometer (Roche Diagnostics Ltd) avoids several methodological problems of the original platelet aggregometers. Whole blood (300 μl) is mixed with set concentrations of collagen, arachidonic acid, ADP, thrombin receptor activator peptide 6 or ristocetin in a single-use plastic cup with a pair of electrodes and a stirring bar. Platelet adhesion and aggregation change electrical impedance between the electrodes. The changing impedance characterises the aggregation velocity, the maximum aggregation and the area under the aggregation curve. This device can detect the effects of anti-platelet drugs [80–82] and changes in platelet function after cardiac surgery [81, 83]. Impedance aggregometry could help diagnose causes of acute bleeding [84, 85]. However, it has not been validated for low platelet counts and, thus, its use in haemorrhagic thrombocytopaenia has yet to be determined. Blood samples drawn for platelet function tests have to be handled carefully, withdrawn without stasis and rested for a set time before adding anticoagulant to the test cuvette, without cooling or freezing the sample.

Other platelet monitoring techniques are currently under development but have not yet been tested during the assessment of platelet-related peri-operative bleeding.

Conclusion

In conclusion, pre-operative anaemia should be detected, classified and treated before major elective procedures and while emergency cases are prepared for surgery. Anaemia should be treated with iron and erythropoiesis-stimulating agents, as appropriate. Blood transfusions should be reserved for severely anaemic patients, particularly with poor physiological reserve, when time does not permit standard treatment. Intravenous iron is safe, reduces blood transfusions and hastens recovery. A combination of pre-operative iron and erythropoiesis-stimulating agents is justified for both elective and urgent surgery, particularly for anaemia with an inflammatory component, although the minimal effective dose is presently unknown.

Standardised questionnaires should be used to gauge the bleeding history instead of routine global coagulation screening. An abnormal history of bleeding, with or without drugs, should trigger further tests of plasmatic haemostasis and platelet function if the patient is scheduled for surgery with a high risk of bleeding or when there is a relevant co-morbidity. Pre-operative platelet functional assessment should be used when indicated. The value of point-of-care coagulation testing in patients with bleeding disorders and that of genetic testing for evaluating bleeding risk deserves further research.

Competing interests

MM has received honoraria for consultancy, lectures and travel from Stryker Ibérica (Spain), Wellspect HealthCare (Sweden), Ferrer Pharma (Spain), Roche (Spain), Vifor Pharma (Spain and Switzerland), PharmaCosmos (Denmark) and Zambon (Spain), but not for this work. SK-L has received honoraria for lecturing and funding for the academic, non-profit educational e-learning platform http://www.peri-operativebleeding.org, from companies involved in peri-operative coagulation monitoring (Roche, TEM International). SG-R has nothing to declare.

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