British Journal of Anaesthesia **106** (1): 13–22 (2011)
doi:10.1093/bja/aeq361

BJA

Detection, evaluation, and management of preoperative anaemia in the elective orthopaedic surgical patient: NATA guidelines

L. T. Goodnough[1*], A. Maniatis[2], P. Earnshaw[3], G. Benoni[4], P. Beris[5], E. Bisbe[6], D. A. Fergusson[7], H. Gombotz[8], O. Habler[9], T. G. Monk[10], Y. Ozier[11], R. Slappendel[12] and M. Szpalski[13]

[1] Department of Pathology and Medicine, Stanford University School of Medicine, Pasteur Dr., Room H-1402, 5626, Stanford, CA 94305, USA
[2] Hematology Division, Henry Dunant Hospital, Athens, Greece
[3] Department of Orthopaedics, Guy's and St Thomas' Hospital, London, UK
[4] Department of Orthopedics, Malmö University Hospital, Malmö, Sweden
[5] Department of Hematology, Geneva University Hospital, Geneva, Switzerland
[6] Department of Anesthesiology, University Hospital Mar-Esperança, Barcelona, Spain
[7] University of Ottawa Centre for Transfusion Research, Ottawa, Ontario, Canada
[8] Department of Anesthesiology and Intensive Care, General Hospital Linz, Linz, Austria
[9] Department of Anesthesiology, Surgical Intensive Care and Pain Control, Krankenhaus Nordwest GmbH, Frankfurt am Main, Germany
[10] Department of Anesthesiology, Duke University Medical Center, Durham, NC, USA
[11] Department of Anesthesiology and Intensive Care, Cochin Hospital, Paris Descartes University, Paris, France
[12] Perioperative Medicine Consultancy, Nijmegen, The Netherlands
[13] Department of Orthopedics, IRIS South Teaching Hospitals, Free University of Brussels, Brussels, Belgium

* Corresponding author. E-mail: ltgoodno@stanford.edu

Editor's key points

- Preoperative anaemia is a serious but treatable condition.
- Preoperative haemoglobin measurement (28 days) should allow time for treatment.
- Abnormalities should be investigated and treated before operation.
- An algorithm to guide management is proposed.

Summary. Previously undiagnosed anaemia is common in elective orthopaedic surgical patients and is associated with increased likelihood of blood transfusion and increased perioperative morbidity and mortality. A standardized approach for the detection, evaluation, and management of anaemia in this setting has been identified as an unmet medical need. A multidisciplinary panel of physicians was convened by the Network for Advancement of Transfusion Alternatives (NATA) with the aim of developing practice guidelines for the detection, evaluation, and management of preoperative anaemia in elective orthopaedic surgery. A systematic literature review and critical evaluation of the evidence was performed, and recommendations were formulated according to the method proposed by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group. We recommend that elective orthopaedic surgical patients have a haemoglobin (Hb) level determination 28 days before the scheduled surgical procedure if possible (Grade 1C). We suggest that the patient's target Hb before elective surgery be within the normal range, according to the World Health Organization criteria (Grade 2C). We recommend further laboratory testing to evaluate anaemia for nutritional deficiencies, chronic renal insufficiency, and/or chronic inflammatory disease (Grade 1C). We recommend that nutritional deficiencies be treated (Grade 1C). We suggest that erythropoiesis-stimulating agents be used for anaemic patients in whom nutritional deficiencies have been ruled out, corrected, or both (Grade 2A). Anaemia should be viewed as a serious and treatable medical condition, rather than simply an abnormal laboratory value. Implementation of anaemia management in the elective orthopaedic surgery setting will improve patient outcomes.

Keywords: anaemia; blood transfusion; orthopaedic surgery; preoperative assessment; preoperative preparation

The overall prevalence of anaemia in the general population increases with age, so that in the elderly (>65 yr old), the prevalence of anaemia as defined by the World Health Organization (WHO)[1] is 11% and 10.2% for men and women, respectively.[2] Previously undiagnosed anaemia is therefore common in elective surgical patients;[3] the prevalence depending on age and associated co-morbidities such as diabetes, congestive heart failure, and other inflammatory conditions. In a US national audit of patients undergoing elective orthopaedic surgery,[4] 35% of the patients

were found to have haemoglobin (Hb) levels <13 g dl^{-1} at preadmission testing. Many of these patients are women and approximately one-third of these are the result of iron deficiency.[2 5 6] Similarly, in a large single-institution study in Spain, preoperative Hb was <13 g dl^{-1} in 19.4% of the patients, and the prevalence of haematinic deficiencies was 33% for iron, 12.3% for vitamin B_{12}, and 3% for folate.[7] These results were also corroborated by a large series from Egypt and Scotland.[8] The remaining anaemias are attributed to chronic inflammatory disease, chronic renal disease (CKD), or unknown causes.[2 9]

Preoperative anaemia is associated with increased morbidity[10 11] and mortality[10 12 13] after orthopaedic surgery, and exposure to allogeneic blood transfusions.[14–16] Admission Hb levels have also been shown to have an impact on postoperative functional recovery in an elderly population with hip fractures[11 17 18] and on the quality of life after total hip arthroplasty.[19]

Background

Impact of preoperative anaemia on clinical outcomes

The impact of preoperative anaemia on perioperative mortality can be illustrated in Jehovah's Witness patients (who refuse allogeneic transfusion for religious reasons) undergoing surgery. In a retrospective study of 1958 Jehovah's Witness patients undergoing non-cardiac surgery, a preoperative Hb concentration of ≤ 10 g dl^{-1} was associated with a significant increase in perioperative mortality.[10] This increase was significantly more pronounced in patients with cardiovascular disease (CVD) than in patients without known CVD. A decrease in Hb of ≤ 2 g dl^{-1} in the absence of CVD was not associated with an increased risk of postoperative death. The risk of death was highest in patients with CVD along with a ≥ 4 g dl^{-1} or greater decline in Hb. In a subsequent analysis, for all patients, postoperative Hb levels ≥ 7 g dl^{-1} were associated with some morbidity but no mortality; but for every 1 g dl^{-1} decrement below 7 g dl^{-1}, mortality risk increased by a factor of 1.5.[20]

In patients accepting allogeneic transfusion, preoperative anaemia is a significant predictor for the likelihood of perioperative blood transfusion.[14 21] Blood transfusion itself is associated with postoperative morbidity and mortality, so that independent analysis of the effects of preoperative anaemia, perioperative blood transfusions, and postoperative anaemia outcomes becomes complex. Nevertheless, in a large retrospective analysis of 300 000 elderly patients undergoing non-cardiac surgery, a preoperative haematocrit of $\leq 39\%$ was associated with a statistically significant increase in 30-day postoperative mortality.[13] This finding was confirmed by a subsequent retrospective study of 8000 patients undergoing non-cardiac surgery, in which 40% of the patients had preoperative anaemia, which was associated with a five-fold increase in 90-day postoperative mortality.[12]

The clinical significance of postoperative anaemia

Inflammatory cytokines after surgery and trauma invoke a response characterized by, among other effects, decreased iron uptake from the gastrointestinal tract and iron sequestration in macrophages, along with a diminished erythroid response to erythropoietin and decreased erythropoietin production.[9] Other contributory causes to postoperative anaemia include pre-existing preoperative anaemia and traumatic and surgical blood loss. Added to these is an element of haemodilution occurring as a result of fluid replacement before, during, and after surgery. Normovolaemic haemodilution is well tolerated due to compensatory mechanisms that maintain an adequate myocardial and peripheral tissue oxygenation. On the other hand, hypovolaemic anaemia must be avoided, as the cardiovascular compensatory mechanisms required to maintain oxygen transport in the setting of anaemia are severely compromised.

Studies in healthy volunteers have shown that Hb concentrations as low as 5 g dl^{-1} in patients with normovolaemia do not result in adverse systemic effects.[22] In patients without CVD who had a preoperative Hb concentration of 6–9 g dl^{-1} and with little further blood loss, the adjusted odds ratio (OR) [95% confidence interval (CI)] for mortality was 1.4 (0.5–4.2) compared with those with a preoperative Hb concentration of >12 g dl^{-1}.[10] However, in patients with CVD and the same degree of anaemia, the corresponding OR was 12.3 (2.5–62.1). This difference persisted through the various strata of preoperative Hb concentrations up to 11 g dl^{-1}. The difference in mortality between patients with and without CVD was even greater for patients with a higher blood loss. Patients with more severe illness had a greater incidence of adverse clinical outcomes (death, infection, etc.) than less ill patients, independent of any potential adverse effect related to blood transfusion.[23]

There is evidence that postoperative anaemia is associated with adverse cardiovascular events. Episodes of perioperative myocardial ischaemia on ECG monitoring in patients undergoing radical prostatectomy were related to both the heart rate and haematocrit levels $<28\%$.[24] A study of high-risk vascular patients undergoing arterial bypass procedures found similar results: a haematocrit $<28\%$ was significantly associated with myocardial ischaemia and other cardiac events.[25] The impact of a conservative (transfusion trigger, Hb 8 g dl^{-1}) or liberal (Hb 10 g dl^{-1}) transfusion strategy on silent myocardial ischaemic episodes in knee and hip arthroplasties found no significant difference between the two groups concerning the overall ischaemic load.[26] However, in patients who did experience postoperative ischaemic episodes, they were significantly prolonged in the liberal group. Neither did they find any temporal relationship between ischaemia and transfusion levels or lowest Hb concentrations. One drawback of the study was that the difference between the mean postoperative Hb concentrations in the two groups was rather small (9.9 and 11.1 g dl^{-1}).[26]

Higher perioperative Hb concentrations in patients with hip fracture were reported to be associated with shorter

length of hospital stay but not with functional independence motor mobility.[17] Overall, postoperative transfusion reduced the risk of readmission but did not improve mobility or reduce mortality. In a pilot study of 84 patients with hip fracture,[27] patients with Hb concentrations <10 g dl^{-1} were randomized to receive blood transfusion either to achieve a symptomatic transfusion trigger (symptomatic anaemia or Hb <8 g dl^{-1}) or to achieve threshold transfusions (sufficient to keep Hb >10 g dl^{-1}). The 60-day mortality was 11.9% in the symptomatic group and 4.8% in the threshold group [relative risk (RR) 2.5; 95% CI, 0.5–12.2], thus favouring a more aggressive transfusion therapy. Other outcomes were similar between the two groups. However, a previous retrospective cohort study of 8787 hip fracture patients[28] found that perioperative transfusion to patients with Hb concentrations 8 g dl^{-1} or higher did not influence 30- or 90-day mortality after adjustment for CVD and other risk factors for death. Recently, a randomized trial of 120 patients found that patients transfused at higher Hb targets (10 g dl^{-1}) had fewer cardiovascular events and lower mortality than those at lower Hb targets.[29] A multicentre trial comparing 'aggressive' and 'conservative' blood transfusion therapy is in progress to address these conflicting data.[23]

The largest randomized trial to evaluate transfusion triggers to date is in 838 intensive care patients, including those undergoing surgery.[30] Patients were randomized either to a restrictive transfusion strategy in which patients received transfusions to keep Hb between 7 and 9 g dl^{-1} or a liberal strategy with Hb levels maintained between 10 and 12 g dl^{-1}. The 30-day mortality in the two groups was not different, 18.7% and 23.3%, respectively ($P=0.11$). The rate of myocardial infarction was significantly lower in the restrictive group, 0.7% *vs* 2.9% ($P=0.02$), as was pulmonary oedema, 5.3% *vs* 10.7% ($P=0.02$).

From these studies, it would appear that for patients without CVD, the tolerance for postoperative anaemia is high. In patients with CVD, the tolerance to anaemia is lower and these patients benefit particularly from anaemia management. Otherwise, a restrictive transfusion policy seems equivalent to a liberal policy in terms of mortality, morbidity, and postoperative mobilization. The most effective strategy to avoid postoperative anaemia and transfusion therapy is to identify and correct preoperative anaemia whenever possible.

Because preoperative anaemia in patients undergoing elective orthopaedic surgery is associated with increased likelihood of blood transfusion and increased perioperative morbidity and mortality, a standardized approach for the detection, evaluation, and management of anaemia in this setting has been identified as an unmet medical need.[31–33] Reviews have suggested laboratory evaluations of anaemia based on traditional approaches such as red cell size (mean corpuscular volume) and serum ferritin levels.[34 35] However, recent advances in the molecular biology of iron transport in clinical settings of chronic disease/inflammation now allow more targeted approaches to anaemia evaluation centred on iron-restricted erythropoiesis and proactive management with iron therapy.[36]

Methods

A multidisciplinary panel of physicians with expertise in orthopaedic surgery, orthopaedic anaesthesia, haematology, and epidemiology was convened by the Network for Advancement of Transfusion Alternatives (NATA) with the aim of developing practice guidelines for the detection, evaluation, and management of preoperative anaemia in elective orthopaedic surgery.

A broad, systematic search strategy applied to Medline (1966–January 2010) and the Cochrane Register of Controlled Trials (January 2010 edition) was developed to identify randomized controlled trials and observational studies evaluating the detection, evaluation, and treatment of anaemia in orthopaedic surgery. The Medline database was searched using the MeSH keywords 'anaemia', 'orthopaedics', and 'blood transfusion'. Additional relevant studies not identified from the electronic search were sought by hand searching of bibliographies of relevant identified articles, and *via* consultation of clinical experts in the field. All citation screening and data extraction was performed independently by two reviewers.

After completion of the systematic review and meta-analyses and compilation of the evidence into strategically structured tables by the two primary reviewers, a task force consisting of clinical and methodological experts reviewed findings to assess the evidence and provide appropriate recommendations for clinical practice. These findings were reviewed in the context of two panel meetings, and via both telephone and electronic communication.

Members of the task force assessed the quantity, quality, and consistency of the published evidence according to the method proposed by the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group,[37] using the modified grading system adopted by the American College of Chest Physicians (Fig. 1).[38] The strength of any recommendation depends on two factors: (i) the trade-off between benefits, risks, burden, and cost; and (ii) the confidence in estimates of those benefits and risks (level of evidence). If the trade-off between benefits and risks is clear, the recommendation is strong (Grade 1, 'we recommend'); if the trade-off is less clear—the best action may differ depending on circumstances or patient or society values—the recommendation is weak (Grade 2, 'we suggest'). The evidence supporting the recommendation is graded in three levels according to its methodological strength: high-quality evidence (A), usually from meta-analyses or randomized controlled trials; moderate-quality evidence (B), typically from randomized controlled trials with significant limitations or observational studies with large effects; and low-quality evidence (C), usually from observational studies.[37 38] The key studies supporting the proposed recommendations are listed and annotated in Supplementary Appendix 1. This framework provides

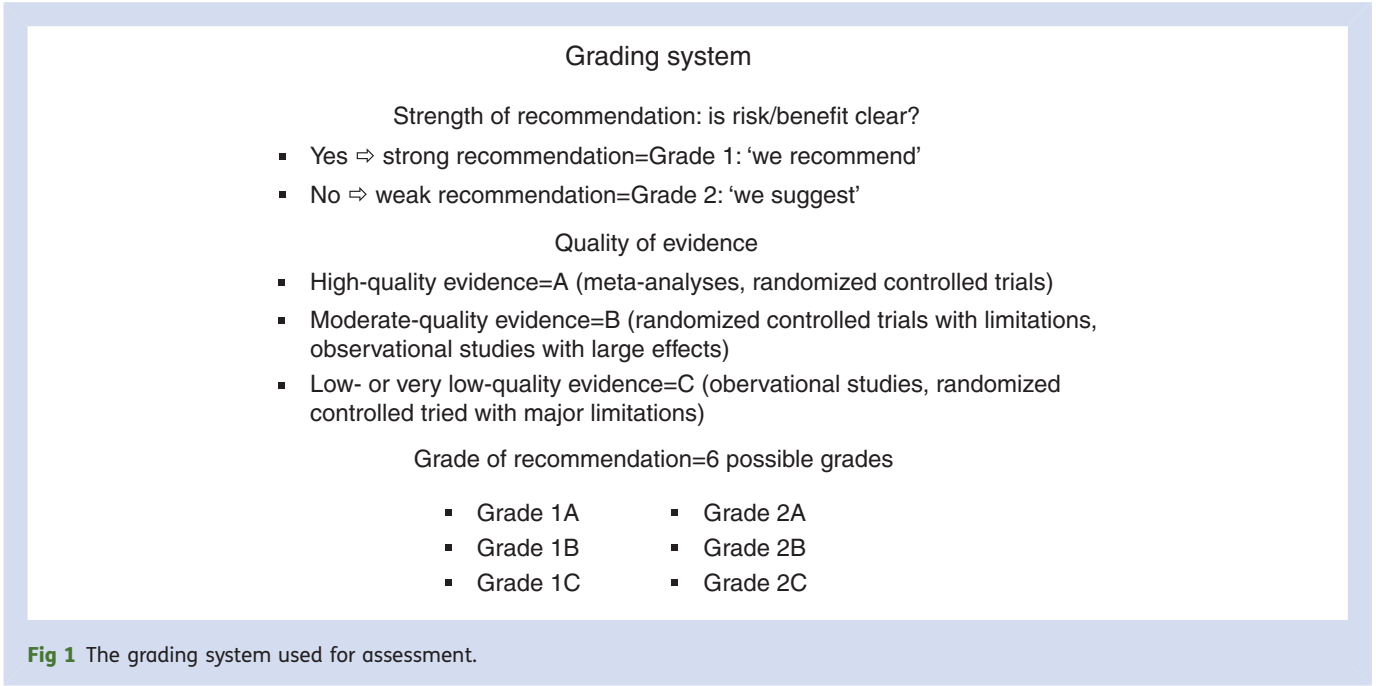

Fig 1 The grading system used for assessment.

reviewers with guidelines to pursue a systematic evaluation of published evidence with the ultimate goal of providing physicians with an informed expert opinion of the state of the evidence for an intervention of interest.

Recommendations

Detection of anaemia

Recommendation 1: We recommend that elective surgical patients have an Hb level determination as close to 28 days before the scheduled surgical procedure as possible (Grade 1C).

The Circular of Information for Blood and Blood Products[33] has recommended that iron, vitamin $B_{12,}$ folic acid, and erythropoietin be used instead of blood transfusion, 'if the clinical condition of the patient permits sufficient time for those agents to promote erythropoiesis . . .' The key phrase relevant to this recommendation is, 'sufficient time . . . to promote erythropoiesis.' Detection of anaemia as close to 28 days before surgery is recommended for sufficient time for evaluation and management.

Recommendation 2: We suggest that the patient's target Hb before elective surgery be within the normal range (female $\geq$12 g dl^{-1}, male $\geq$13 g dl^{-1}), according to the WHO criteria (Grade 2C).

This recommendation is a suggestion, indicating a lack of panel consensus and evidence on whether elective surgical procedures should be cancelled, representing best practices, for patients who are identified to be anaemic. Delay of elective scheduled surgery for definitive evaluation of newly detected anaemia and associated clinical conditions (nutritional deficiency, chronic renal disease, etc.) will benefit patients and reduce harm, including likelihood of exposure to blood transfusions.

Evaluation of anaemia

Recommendation 3: We recommend that laboratory testing be performed to further evaluate anaemia for nutritional deficiencies, chronic renal insufficiency, and/or chronic inflammatory disease (Grade 1C).

Unexplained anaemia should be considered as secondary to some other process,[2 9] and the cause of the anaemia must be evaluated. Laboratory testing must be performed to further evaluate anaemia for nutritional deficiencies, chronic renal insufficiency, and/or chronic inflammatory disease and the cause of the anaemia must be evaluated. If a screening blood count detects anaemia, evaluation should begin with an assessment of iron status. The assessment of iron-restricted erythropoiesis needs to distinguish between absolute iron deficiency, iron sequestration due to inflammation, and/or functional iron deficiency due to erythropoietin stimulation.[39] The accurate differentiation of these is difficult using traditional biochemical markers of iron status, such as serum iron, percentage saturation of transferrin, and serum ferritin.[9] As ferritin is an acute-phase reactant, traditional laboratory thresholds of $<$12 μg $litre^{-1}$ may be suitable for identifying absolute iron deficiency in normal individuals, but not in patients with any evidence of an inflammatory process.[36] Correlation of iron stores with ferritin values has demonstrated that ferritin levels must exceed 30 μg $litre^{-1}$ to achieve a 92% sensitivity for exclusion of absolute iron deficiency.[40] For patients without chronic renal disease, ferritin levels $>$100 μg $litre^{-1}$ confirm the presence of stored iron.[9 36]

When absolute iron deficiency is detected, referral to a gastroenterologist to rule out a gastrointestinal malignancy as a source of chronic blood loss is indicated.[38] If laboratory evaluation or a diagnostic trial of iron therapy rules out absolute iron deficiency, measurement of serum creatinine

and glomerular filtration rate (GFR) may indicate CKD and the need for referral to a nephrologist. If ferritin, iron saturation values, or both or other markers of iron-restricted erythropoiesis are inconclusive, further evaluation to rule out iron deficiency or iron sequestration due to inflammation/chronic disease is necessary. A therapeutic trial of oral iron therapy would confirm absolute iron deficiency. No response to iron therapy may not rule out absolute iron deficiency because of patient non-compliance,[39] ongoing blood (iron) losses in excess of oral iron absorption,[40] and/or diminished gastrointestinal absorption of iron due to inflammation.[9] Additionally, iron-restricted erythropoiesis due to iron sequestration, functional deficiency, or both must be considered. In these instances, management strategies that include i.v. iron, with or without erythropoiesis-stimulating agents (ESA) therapy, should be considered.[41]

Management of anaemia

Treatment of nutritional deficiencies

Recommendation 4: We recommend that nutritional deficiencies be treated (Grade 1C).

Nutritional deficiencies must be treated. Iron supplementation is indicated in the presence of confirmed iron deficiency anaemia. The effectiveness of oral iron in the management of preoperative anaemia has been demonstrated in patients undergoing orthopaedic[41 42] and colorectal cancer[43 44] surgery. In the absence of preoperative iron supplementation, postoperative iron supplementation has not been shown to be effective.[45–49]

Three small series of orthopaedic surgery patients, undergoing repair of hip fracture[50 51] or joint replacement and back surgery,[52] demonstrated the feasibility of parenteral iron supplementation in the preoperative management of iron-deficiency anaemia, particularly if there was a short interval before surgery. An expert panel recently reviewed the role of i.v. iron in the management of perioperative anaemia and concluded that patients with preoperative anaemia due to iron deficiency or chronic disease should receive preoperative treatment with oral or i.v. iron, depending on the timescale before surgery, tolerance of oral iron, and iron status.[53]

Stimulation of erythropoiesis

Recommendation 5: We suggest that ESA be used for anaemic patients in whom nutritional deficiencies have been ruled out, corrected, or both (Grade 2A).

The use of ESA therapy in patients undergoing major, elective surgery is well established on the basis of controlled, randomized trials and is approved for use in this setting. However, recent concerns regarding the RR/benefit of these agents and their appropriate use in patients with chronic renal disease,[54–61] in patients with anaemia related to cancer or chemotherapy,[62–70] and in patients undergoing elective surgery[71] have resulted in a Grade 2 or 'suggested' recommendation.

The use of ESAs in patients with anaemia undergoing elective orthopaedic (hip, knee, and spine) surgery was reviewed under the auspices of NATA.[72] A meta-analysis of 41 published studies [eight studies of ESA alone,[71 73–79] 22 studies of ESA augmented with preoperative autologous blood donation (PABD),[39 80–100] seven studies of ESA compared with PABD,[71 84 101–105] and four studies of ESA and other comparators][106–109] was performed. Pooled estimates of transfusion exposure demonstrated clinically important benefit for both rHuEPO alone (RR, 0.44; 95% CI, 0.31–0.64) and rHuEPO augmented by PABD (RR, 0.61; 95% CI, 0.49–0.75). Although sufficient data were available for patients undergoing hip surgery, a large number of studies performed in patients undergoing a mixture of surgical procedures, and a failure to report indication-specific associations with the intervention, limit the ability to make judgement on the effectiveness of rHuEPO in patients undergoing non-hip procedures such as knee and spinal surgery. Taking account of all the studies, the risk of deep vein thrombosis was increased with the use of rHuEPO [Peto OR of 1.66 (95% CI 1.10–2.48)] but was inconclusive on the risk of mortality, myocardial infarction, and cerebrovascular accidents due to their low incidence.

Anaemia of chronic disease is a diagnosis of exclusion.[7] However, the following are considered evidence of anaemia of chronic disease: anaemia with no evidence of nutritional deficiencies or chronic renal disease, and the presence of an associated chronic disease. In the presence of a low Hb and normal mean corpuscular volume, a reticulocyte count and serum creatinine level should be measured and GFR calculated. A nephrology consultation is appropriate if an abnormal creatinine level or GFR is present to evaluate for possible haemolysis, blood loss, or chronic renal disease.

Patients should receive iron supplementation throughout the course of ESA therapy, to optimize the dose–response relationship for ESA therapy and red blood cell production in the pre-surgical setting.[110] ESA therapy with iron supplementation is effective in reducing subsequent need for allogeneic transfusion.[72]

Detection, evaluation, and management of preoperative of anaemia: an algorithm

We propose an algorithm for the detection, evaluation, and management of preoperative anaemia based on the above recommendations (Fig. 2).

If anaemia is detected on a screening sample, evaluation is necessary and begins with an assessment of iron status. If serum ferritin, transferrin saturation levels, or both indicate absolute iron deficiency, referral to a gastroenterologist to rule out a gastrointestinal malignancy as a source of chronic blood loss may be indicated.

If serum ferritin, transferrin saturation values, or both rule out absolute iron deficiency, serum creatinine and GFR determination may indicate CKD and the need for referral to a nephrologist.

When serum ferritin, transferrin saturation values, or both are inconclusive, further evaluation to rule out absolute iron deficiency or inflammation/chronic disease is necessary. A

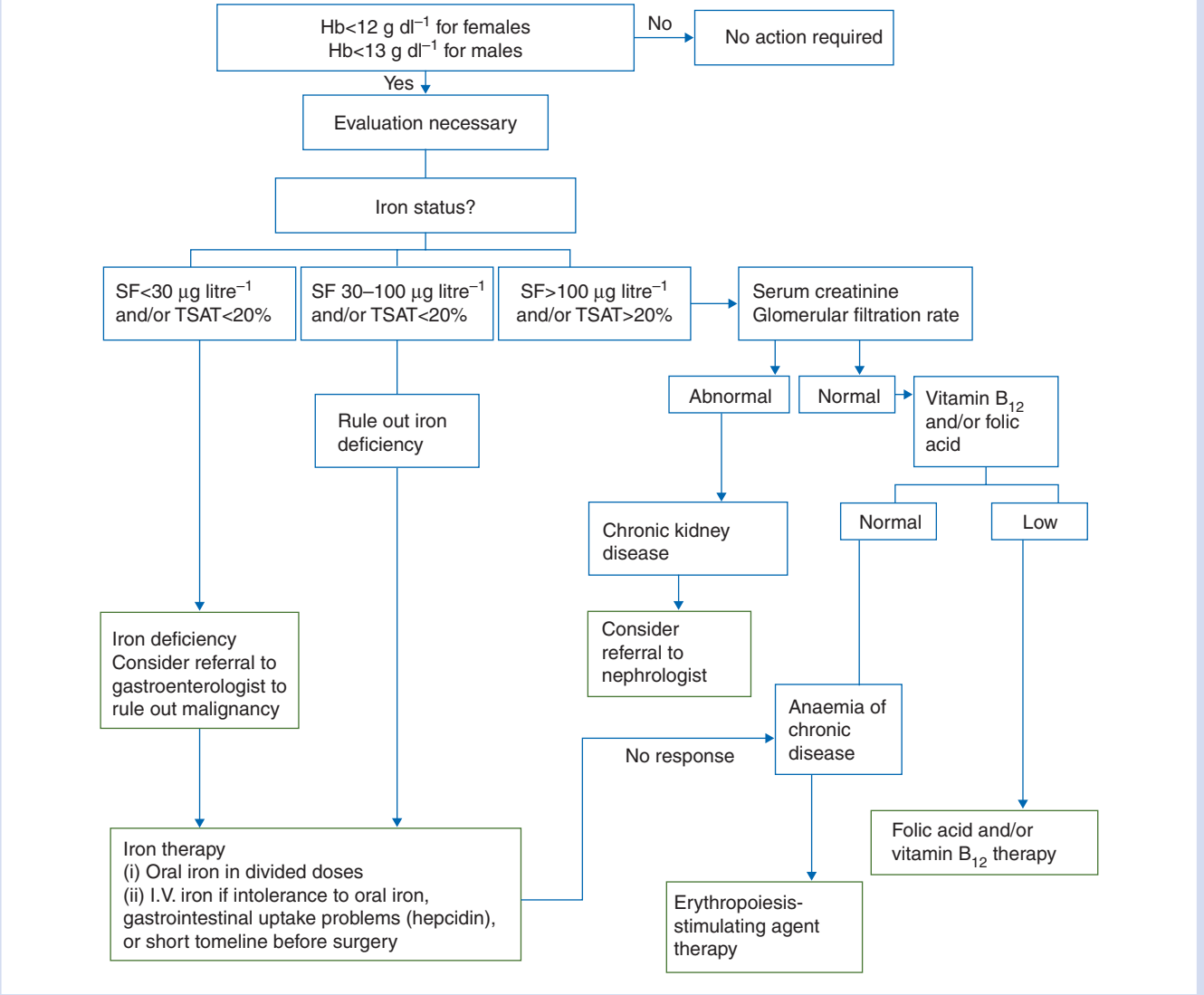

Fig 2 Proposed algorithm for the detection, evaluation, and management of preoperative anaemia. SF, serum ferritin; TSAT, transferrin saturation.

therapeutic trial of iron would confirm absolute iron deficiency. No response to iron therapy would indicate the anaemia of chronic disease, suggesting that ESA therapy be initiated.

These recommendations are intended to provide guidance for preoperative evaluation in the elective surgical patient. Limiting preadmission testing to a few days before the scheduled operative procedure precludes the opportunity to evaluate and manage the patient with unexplained anaemia. The recommended time frame of testing 4 weeks before the scheduled elective procedure ensures that anaemia can be detected, evaluated, and managed appropriately before elective surgery.

Anaemia should be viewed as a serious and treatable medical condition, rather than as simply an abnormal laboratory value. Anaemia is a common condition in surgical patients and is independently associated with increased mortality. The diagnosis of an unexpected anaemia in patients undergoing elective surgery in which significant blood loss is anticipated should be considered an indication for rescheduling surgery until the evaluation is completed. The presence of preoperative anaemia is significantly associated with morbidity and mortality after surgery, thus warranting this recommendation. Treatment of postoperative anaemia should be the focus of investigations for the reduction of perioperative risk. We conclude that implementation of anaemia management in the elective surgery setting will improve patient outcome.

Supplementary material

Supplementary material is available at *British Journal of Anaesthesia* online.

Acknowledgements

We gratefully acknowledge the assistance of François Christory and Jason Calcagno in preparation of this manuscript.

Conflict of interest

L.T.G. is a consultant for AMAG Pharmaceuticals, Amgen, CSL Behring, Eli Lilly, Luitpold Pharmaceuticals, Ortho Biotech and Watson Pharmaceuticals; E.B. has received speaking honoraria from Janssen-Cilag and Vifor; Y.O.'s department has received funding from Janssen-Cilag; all other authors declare no conflict of interest.

Funding

This project was funded by the Network for the Advancement of Transfusion Alternatives (NATA), who received an educational grant from Janssen Pharmaceutica NV. Medical Education Global Solutions organized the expert meetings and coordinated the project on behalf of NATA.

References

1 Nutritional anaemias. Report of a WHO scientific group. World Health Organization Technical Report Series No. 405. Geneva: World Health Organization, 1968

2 Guralnik JM, Eisenstaedt RS, Ferrucci L, *et al.* Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood* 2004; **104**: 2263–8

3 Goodnough LT, Nissenson AR, Dubois RW. Anemia: not just an innocent bystander? *Arch Intern Med* 2003; **163**: 1400–4

4 Bierbaum BE, Callaghan JJ, Galante JO, *et al.* An analysis of blood management in patients having a total hip or knee arthroplasty. *J Bone Joint Surg Am* 1999; **81**: 2–10

5 Guyatt GH, Patterson C, Ali M, *et al.* Diagnosis of iron-deficiency anemia in the elderly. *Am J Med* 1990; **88**: 205–9

6 Wilson A, Yu HT, Goodnough LT, Nissenson AR. Prevalence and outcomes of anemia in rheumatoid arthritis: a systematic review of the literature. *Am J Med* 2004; **116**(Suppl. 7A): 50–7S

7 Bisbe E, Castillo J, Sáez M, *et al.* Prevalence of preoperative anemia and hematinic deficiencies in patients scheduled for elective major orthopedic surgery. *Transfus Alternat Transfus Med* 2008; **10**: 166–73

8 Saleh E, McClelland DB, Hay A, *et al.* Prevalence of anaemia before major joint arthroplasty and the potential impact of preoperative investigation and correction on perioperative blood transfusions. *Br J Anaesth* 2007; **99**: 801–8

9 Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; **352**: 1011–23

10 Carson JL, Duff A, Poses RM, *et al.* Effect of anaemia and cardiovascular disease on surgical mortality and morbidity. *Lancet* 1996; **348**: 1055–60

11 Gruson KI, Aharonoff GB, Egol KA, *et al.* The relationship between admission hemoglobin level and outcome after hip fracture. *J Orthop Trauma* 2002; **16**: 39–44

12 Beattie WS, Karkouti K, Wijeysundera DN, Tait G. Risk associated with preoperative anemia in noncardiac surgery: a single-center cohort study. *Anesthesiology* 2009; **110**: 574–81

13 Wu WC, Schifftner TL, Henderson WG, *et al.* Preoperative hematocrit levels and postoperative outcomes in older patients undergoing noncardiac surgery. *J Am Med Assoc* 2007; **297**: 2481–8

14 Khanna MP, Hebert PC, Fergusson DA. Review of the clinical practice literature on patient characteristics associated with perioperative allogeneic red blood cell transfusion. *Transfus Med Rev* 2003; **17**: 110–9

15 Shander A, Knight K, Thurer R, *et al.* Prevalence and outcomes of anemia in surgery: a systematic review of the literature. *Am J Med* 2004; **116**(Suppl. 7A): 58–69S

16 Gruson KI, Accousti KJ, Parsons BO, *et al.* Transfusion after shoulder arthroplasty: an analysis of rates and risk factors. *J Shoulder Elbow Surg* 2009; **18**: 225–30

17 Halm EA, Wang JJ, Boockvar K, *et al.* The effect of perioperative anemia on clinical and functional outcomes in patients with hip fracture. *J Orthop Trauma* 2004; **18**: 369–74

18 Lawrence VA, Silverstein JH, Cornell JE, *et al.* Higher Hb level is associated with better early functional recovery after hip fracture repair. *Transfusion* 2003; **43**: 1717–22

19 Conlon NP, Bale EP, Herbison GP, McCarroll M. Postoperative anemia and quality of life after primary hip arthroplasty in patients over 65 years old. *Anesth Analg* 2008; **106**: 1056–61

20 Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion* 2002; **42**: 812–8

21 Myers E, O'Grady P, Dolan AM. The influence of preclinical anaemia on outcome following total hip replacement. *Arch Orthop Trauma Surg* 2004; **124**: 699–701

22 Weiskopf RB, Viele MK, Feiner J, *et al.* Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *J Am Med Assoc* 1998; **279**: 217–21

23 Carson JL, Terrin ML, Magaziner J, *et al.* Transfusion trigger trial for functional outcomes in cardiovascular patients undergoing surgical hip fracture repair (FOCUS). *Transfusion* 2006; **46**: 2192–206

24 Hogue CW Jr, Goodnough LT, Monk TG. Perioperative myocardial ischemic episodes are related to hematocrit level in patients undergoing radical prostatectomy. *Transfusion* 1998; **38**: 924–31

25 Nelson AH, Fleisher LA, Rosenbaum SH. Relationship between postoperative anemia and cardiac morbidity in high-risk vascular patients in the intensive care unit. *Crit Care Med* 1993; **21**: 860–6

26 Grover M, Talwalkar S, Casbard A, *et al.* Silent myocardial ischaemia and haemoglobin concentration: a randomized controlled trial of transfusion strategy in lower limb arthroplasty. *Vox Sang* 2006; **90**: 105–12

27 Carson JL, Terrin ML, Barton FB, *et al.* A pilot randomized trial comparing symptomatic vs. hemoglobin-level-driven red blood cell transfusions following hip fracture. *Transfusion* 1998; **38**: 522–9

28 Carson JL, Duff A, Berlin JA, *et al.* Perioperative blood transfusion and postoperative mortality. *J Am Med Assoc* 1998; **279**: 199–205

29 Foss NB, Kristensen MT, Jensen PS, *et al.* The effects of liberal versus restrictive transfusion thresholds on ambulation after hip fracture surgery. *Transfusion* 2009; **49**: 227–34

30 Hébert PC, Wells G, Blajchman MA, *et al.* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med* 1999; **340**: 409–17

31 Goodnough LT, Monk TG, Andriole GL. Erythropoietin therapy. *N Engl J Med* 1997; **336**: 933–8

32 Mercuriali F, Inghilleri G. Management of preoperative anaemia. *Br J Anaesth* 1998; **81**(Suppl. 1): 56–61

33 *Circular of Information for the Use of Human Blood and Blood Components*. Bethesda, MD: American Association of Blood Banks, 2000.

34 Goodnough LT, Shander A, Spivak JL, *et al.* Detection, evaluation, and management of anemia in the elective surgical patient. *Anesth Analg* 2005; **101**: 1858–61

35 Goodnough LT, Maniatis A, Earnshaw P. Management of preoperative anaemia in patients undergoing elective surgery. *ISBT Sci Ser* 2010; **5**: 120–4

36 Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. *Blood* 2010 Sept. 8 [Epub ahead of print]

37 Atkins D, Best D, Briss PA, *et al.* Grading quality of evidence and strength of recommendations. *Br Med J* 2004; **328**: 1490

38 Guyatt GH, Cook DJ, Jaeschke R, *et al.* Grades of recommendation for antithrombotic agents: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; **133**: 123–31S

39 Mercuriali F, Zanella A, Barosi G, *et al.* Use of erythropoietin to increase the volume of autologous blood donated by orthopedic patients. *Transfusion* 1993; **33**: 55–60

40 Mast AE, Blinder MA, Gronowski AM, *et al.* Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem* 1998; **44**: 45–51

41 Andrews CM, Lane DW, Bradley JG. Iron pre-load for major joint replacement. *Transfus Med* 1997; **7**: 281–6

42 Cuenca J, Garcia-Erce JA, Martinez F, *et al.* Preoperative haematinics and transfusion protocol reduce the need for transfusion after total knee replacement. *Int J Surg* 2007; **5**: 89–94

43 Lidder PG, Sanders G, Whitehead E, *et al.* Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery—a prospective, randomised, controlled trial. *Ann R Coll Surg Engl* 2007; **89**: 418–21

44 Okuyama M, Ikeda K, Shibata T, *et al.* Preoperative iron supplementation and intraoperative transfusion during colorectal cancer surgery. *Surg Today* 2005; **35**: 36–40

45 Mundy GM, Birtwistle SJ, Power RA. The effect of iron supplementation on the level of haemoglobin after lower limb arthroplasty. *J Bone Joint Surg Br* 2005; **87**: 213–7

46 Sutton PM, Cresswell T, Livesey JP, *et al.* Treatment of anaemia after joint replacement. A double-blind, randomised, controlled trial of ferrous sulphate versus placebo. *J Bone Joint Surg Br* 2004; **86**: 31–3

47 Weatherall M, Maling TJ. Oral iron therapy for anaemia after orthopaedic surgery: randomized clinical trial. *ANZ J Surg* 2004; **74**: 1049–51

48 Zauber NP, Zauber AG, Gordon FJ, *et al.* Iron supplementation after femoral head replacement for patients with normal iron stores. *J Am Med Assoc* 1992; **267**: 525–7

49 Parker MJ. Iron supplementation for anemia after hip fracture surgery: a randomized trial of 300 patients. *J Bone Joint Surg Am* 2010; **92**: 265–9

50 Cuenca J, Garcia-Erce JA, Munoz M, *et al.* Patients with pertrochanteric hip fracture may benefit from preoperative intravenous iron therapy: a pilot study. *Transfusion* 2004; **44**: 1447–52

51 Cuenca J, Garcia-Erce JA, Martinez AA, *et al.* Role of parenteral iron in the management of anaemia in the elderly patient undergoing displaced subcapital hip fracture repair: preliminary data. *Arch Orthop Trauma Surg* 2005; **125**: 342–7

52 Theusinger OM, Leyvraz PF, Schanz U, *et al.* Treatment of iron deficiency anemia in orthopedic surgery with intravenous iron: efficacy and limits: a prospective study. *Anesthesiology* 2007; **107**: 923–7

53 Beris P, Munoz M, Garcia-Erce JA, *et al.* Perioperative anaemia management: consensus statement on the role of intravenous iron. *Br J Anaesth* 2008; **100**: 599–604

54 Besarab A, Bolton WK, Browne JK, *et al.* The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. *N Engl J Med* 1998; **339**: 584–90

55 Drueke TB, Locatelli F, Clyne N, *et al.* Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med* 2006; **355**: 2071–84

56 Singh AK, Szczech L, Tang KL, *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; **355**: 2085–98

57 Pfeffer MA, Burdmann EA, Chen CY, *et al.* A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med* 2009; **361**: 2019–32

58 Palmer SC, Navaneethan SD, Craig JC, *et al.* Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med* 2010; **153**: 23–33

59 KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis* 2007; **50**: 471–530

60 Locatelli F, Nissenson AR, Barrett BJ, *et al.* Clinical practice guidelines for anemia in chronic kidney disease: problems and solutions. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2008; **74**: 1237–40

61 Locatelli F, Covic A, Eckardt KU, *et al.* Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP). *Nephrol Dial Transplant* 2009; **24**: 348–54

62 Henke M, Laszig R, Rube C, *et al.* Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. *Lancet* 2003; **362**: 1255–60

63 Leyland-Jones B, Semiglazov V, Pawlicki M, *et al.* Maintaining normal hemoglobin levels with epoetin alfa in mainly nonanemic patients with metastatic breast cancer receiving first-line chemotherapy: a survival study. *J Clin Oncol* 2005; **23**: 5960–72

64 Bokemeyer C, Aapro MS, Courdi A, *et al.* EORTC guidelines for the use of erythropoietic proteins in anaemic patients with cancer: 2006 update. *Eur J Cancer* 2007; **43**: 258–70

65 Aapro MS, Link H. September 2007 update on EORTC guidelines and anemia management with erythropoiesis-stimulating agents. *Oncologist* 2008; **13**(Suppl. 3): 33–6

66 Rizzo JD, Somerfield MR, Hagerty KL, *et al.* Use of epoetin and darbepoetin in patients with cancer: 2007 American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update. *Blood* 2008; **111**: 25–41

67 Bennett CL, Silver SM, Djulbegovic B, *et al.* Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia. *J Am Med Assoc* 2008; **299**: 914–24

68 Bohlius J, Schmidlin K, Brillant C, *et al.* Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: a meta-analysis of randomised trials. *Lancet* 2009; **373**: 1532–42

69 Tonelli M, Hemmelgarn B, Reiman T, *et al.* Benefits and harms of erythropoiesis-stimulating agents for anemia related to cancer: a meta-analysis. *Can Med Assoc J* 2009; **180**: E62–71

70 Adamson JW. Erythropoietic-stimulating agents: the cancer progression controversy and collateral damage to the blood supply. *Transfusion* 2009; **49**: 824–6

71 Stowell CP, Chandler H, Jove M, *et al.* An open-label, randomized study to compare the safety and efficacy of perioperative

epoetin alfa with preoperative autologous blood donation in total joint arthroplasty. *Orthopedics* 1999; **22**: s105–12

72 Fergusson DA, Hutton B, Maniatis A, *et al.* Use of recombinant human erythropoietin in orthopaedic surgery: a systematic review (submitted for publication)

73 Canadian Orthopedic Perioperative Erythropoietin Study Group. Effectiveness of perioperative recombinant human erythropoietin in elective hip replacement. *Lancet* 1993; **341**: 1227–32

74 de Andrade JR, Jove M, Landon G, *et al.* Baseline hemoglobin as a predictor of risk of transfusion and response to Epoetin alfa in orthopedic surgery patients. *Am J Orthop* 1996; **25**: 533–42

75 Faris PM, Ritter MA, Abels RI. The effects of recombinant human erythropoietin on perioperative transfusion requirements in patients having a major orthopaedic operation. The American Erythropoietin Study Group. *J Bone Joint Surg Am* 1996; **78**: 62–72

76 Feagan BG, Wong CJ, Kirkley A, *et al.* Erythropoietin with iron supplementation to prevent allogeneic blood transfusion in total hip joint arthroplasty. A randomized, controlled trial. *Ann Intern Med* 2000; **133**: 845–54

77 Green D, Lawler M, Rosen M, *et al.* Recombinant human erythropoietin: effect on the functional performance of anemic orthopedic patients. *Arch Phys Med Rehabil* 1996; **77**: 242–6

78 Olijhoek G, Megens JG, Musto P, *et al.* Role of oral versus IV iron supplementation in the erythropoietic response to rHuEPO: a randomized, placebo-controlled trial. *Transfusion* 2001; **41**: 957–63

79 Weber EW, Slappendel R, Hemon Y, *et al.* Effects of epoetin alfa on blood transfusions and postoperative recovery in orthopaedic surgery: the European Epoetin Alfa Surgery Trial (EEST). *Eur J Anaesthesiol* 2005; **22**: 249–57

80 Aksoy MC, Tokgozoglu AM. Erythropoietin for autologous blood donation in total hip arthroplasty patients. *Arch Orthop Trauma Surg* 2001; **121**: 162–5

81 Avall A, Hyllner M, Bengtson JP, *et al.* Recombinant human erythropoietin in preoperative autologous blood donation did not influence the haemoglobin recovery after surgery. *Acta Anaesthesiol Scand* 2003; **47**: 687–92

82 Baudoux E. Autologous blood donation plus epoetin alfa in nonanemic orthopedic surgery patients. *Semin Hematol* 1996; **33**: 31–2

83 Beris P, Mermillod B, Levy G, *et al.* Recombinant human erythropoietin as adjuvant treatment for autologous blood donation. A prospective study. *Vox Sang* 1993; **65**: 212–8

84 Bezwada HP, Nazarian DG, Henry DH, Booth RE Jr. Preoperative use of recombinant human erythropoietin before total joint arthroplasty. *J Bone Joint Surg Am* 2003; **85-A**: 1795–800

85 Biesma DH, Kraaijenhagen RJ, Marx JJ, van de Wiel A. The efficacy of subcutaneous recombinant human erythropoietin in the correction of phlebotomy-induced anemia in autologous blood donors. *Transfusion* 1993; **33**: 825–9

86 Biesma DH, Marx JJ, Kraaijenhagen RJ, *et al.* Lower homologous blood requirement in autologous blood donors after treatment with recombinant human erythropoietin. *Lancet* 1994; **344**: 367–70

87 Biesma DH, Van de Wiel A, Beguin Y, *et al.* Erythropoietic activity and iron metabolism in autologous blood donors during recombinant human erythropoietin therapy. *Eur J Clin Invest* 1994; **24**: 426–32

88 Cazenave JP, Irrmann C, Waller C, *et al.* Epoetin alfa facilitates presurgical autologous blood donation in non-anaemic patients scheduled for orthopaedic or cardiovascular surgery. *Eur J Anaesthesiol* 1997; **14**: 432–42

89 de Pree C, Mermillod B, Hoffmeyer P, Beris P. Recombinant human erythropoietin as adjuvant treatment for autologous blood donation in elective surgery with large blood needs (> or =5 units): a randomized study. *Transfusion* 1997; **37**: 708–14

90 Goodnough LT, Price TH, Rudnick S, Soegiarso RW. Preoperative red cell production in patients undergoing aggressive autologous blood phlebotomy with and without erythropoietin therapy. *Transfusion* 1992; **32**: 441–5

91 Goodnough LT, Rudnick S, Price TH, *et al.* Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy. *N Engl J Med* 1989; **321**: 1163–8

92 Hasegawa Y, Takamatsu J, Iwase T, *et al.* Effects of recombinant human erythropoietin on thrombosis and fibrinolysis in autologous transfusion for hip surgery. *Arch Orthop Trauma Surg* 1999; **119**: 384–7

93 Mercuriali F, Inghilleri G, Biffi E, *et al.* Epoetin alfa in low hematocrit patients to facilitate autologous blood donation in total hip replacement: a randomized, double-blind, placebo-controlled, dose-ranging study. *Acta Haematol* 1998; **100**: 69–76

94 Price TH, Goodnough LT, Vogler WR, *et al.* The effect of recombinant human erythropoietin on the efficacy of autologous blood donation in patients with low hematocrits: a multicenter, randomized, double-blind, controlled trial. *Transfusion* 1996; **36**: 29–36

95 Sans T, Bofil C, Joven J, *et al.* Effectiveness of very low doses of subcutaneous recombinant human erythropoietin in facilitating autologous blood donation before orthopedic surgery. *Transfusion* 1996; **36**: 822–6

96 Schlaeppi B, Gunter P, Nydegger UE. Enhancing the efficacy of preoperative autologous blood donation by erythropoietin. *Transfus Sci* 1994; **15**: 171–7

97 Shapiro GS, Boachie-Adjei O, Dhawlikar SH, Maier LS. The use of epoetin alfa in complex spine deformity surgery. *Spine* 2002; **27**: 2067–71

98 Tryba M. Epoetin alfa plus autologous blood donation and normovolemic hemodilution in patients scheduled for orthopedic or vascular surgery. *Semin Hematol* 1996; **33**: 34–6; discussion 7–8

99 Tryba M. Epoetin alfa plus autologous blood donation in patients with a low hematocrit scheduled to undergo orthopedic surgery. *Semin Hematol* 1996; **33**: 22–4; discussion 5–6

100 von Bormann B, Weidler B, Friedrich M, von Andrian-Werburg H. Recombinant erythropoietin in autologous blood donation. *Anaesthesist* 1991; **40**: 386–90

101 Deutsch A, Spaulding J, Marcus RE. Preoperative epoetin alfa vs autologous blood donation in primary total knee arthroplasty. *J Arthroplasty* 2006; **21**: 628–35

102 Gombotz H, Gries M, Sipurzynski S, *et al.* Preoperative treatment with recombinant human erythropoietin or predeposit of autologous blood in women undergoing primary hip replacement. *Acta Anaesthesiol Scand* 2000; **44**: 737–42

103 Hardwick ME, Morris BM, Colwell CW Jr. Two-dose epoetin alfa reduces blood transfusions compared with autologous donation. *Clin Orthop Relat Res* 2004; **423**: 240–4

104 Keating EM, Callaghan JJ, Ranawat AS, *et al.* A randomized, parallel-group, open-label trial of recombinant human erythropoietin vs preoperative autologous donation in primary total joint arthroplasty: effect on postoperative vigor and handgrip strength. *J Arthroplasty* 2007; **22**: 325–33

105 Rosencher N, Poisson D, Albi A, *et al.* Two injections of erythropoietin correct moderate anemia in most patients awaiting orthopedic surgery. *Can J Anaesth* 2005; **52**: 160–5

106 Goldberg MA, McCutchen JW, Jove M, *et al.* A safety and efficacy comparison study of two dosing regimens of epoetin alfa in patients undergoing major orthopedic surgery. *Am J Orthop* 1996; **25**: 544–52

107 Mercuriali F, Inghilleri G, Biffi E, *et al.* Comparison between intravenous and subcutaneous recombinant human erythropoietin (epoetin alfa) administration in presurgical autologous blood donation in anemic rheumatoid arthritis patients undergoing major orthopedic surgery. *Vox Sang* 1997; **72**: 93–100

108 Tsutsui H, Sugioka Y, Takaku F, *et al.* A double-blind dose ranging study of weekly subcutaneous administration of rHuEPO (KRN5702) on post-phlebotomy anemia of patients scheduled for predeposit autologous blood transfusion (multicenter late PhII study). *Nippon Seikeigeka Gakkai Zasshi* 1993; **67**: 919–34

109 Moonen AF, Thomassen BJ, Knoors NT, *et al.* Pre-operative injections of epoetin-alpha versus post-operative retransfusion of autologous shed blood in total hip and knee replacement: a prospective randomised clinical trial. *J Bone Joint Surg Br* 2008; **90**: 1079–83

110 Goodnough LT, Skikne B, Brugnara C. Erythropoietin, iron, and erythropoiesis. *Blood* 2000; **96**: 823–33