

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

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## 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)<sup>1</sup> is 11% and 10.2% for men and women, respectively.<sup>2</sup> Previously undiagnosed anaemia is

therefore common in elective surgical patients;<sup>3</sup> 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,<sup>4</sup> 35% of the patients

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

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

## 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  $\leq 10 \text{ g dl}^{-1}$  was associated with a significant increase in perioperative mortality.<sup>10</sup> This increase was significantly more pronounced in patients with cardiovascular disease (CVD) than in patients without known CVD. A decrease in Hb of  $\leq 2 \text{ g dl}^{-1}$  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  $\geq 4 \text{ g dl}^{-1}$  or greater decline in Hb. In a subsequent analysis, for all patients, postoperative Hb levels  $\geq 7 \text{ g dl}^{-1}$  were associated with some morbidity but no mortality; but for every  $1 \text{ g dl}^{-1}$  decrement below  $7 \text{ g dl}^{-1}$ , mortality risk increased by a factor of 1.5.<sup>20</sup>

In patients accepting allogeneic transfusion, preoperative anaemia is a significant predictor for the likelihood of perioperative blood transfusion.<sup>14 21</sup> 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.<sup>13</sup> 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.<sup>12</sup>

### 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.<sup>9</sup> 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  $5 \text{ g dl}^{-1}$  in patients with normovolaemia do not result in adverse systemic effects.<sup>22</sup> In patients without CVD who had a preoperative Hb concentration of  $6\text{--}9 \text{ g dl}^{-1}$  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  $>12 \text{ g dl}^{-1}$ .<sup>10</sup> 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  $11 \text{ g dl}^{-1}$ . 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.<sup>23</sup>

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  $<28\%$ .<sup>24</sup> 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.<sup>25</sup> The impact of a conservative (transfusion trigger, Hb  $8 \text{ g dl}^{-1}$ ) or liberal (Hb  $10 \text{ g dl}^{-1}$ ) 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.<sup>26</sup> 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  $11.1 \text{ g dl}^{-1}$ ).<sup>26</sup>

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.<sup>17</sup> 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,<sup>27</sup> patients with Hb concentrations  $<10$  g dl<sup>-1</sup> were randomized to receive blood transfusion either to achieve a symptomatic transfusion trigger (symptomatic anaemia or Hb  $<8$  g dl<sup>-1</sup>) or to achieve threshold transfusions (sufficient to keep Hb  $>10$  g dl<sup>-1</sup>). 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<sup>28</sup> found that perioperative transfusion to patients with Hb concentrations 8 g dl<sup>-1</sup> 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<sup>-1</sup>) had fewer cardiovascular events and lower mortality than those at lower Hb targets.<sup>29</sup> A multicentre trial comparing 'aggressive' and 'conservative' blood transfusion therapy is in progress to address these conflicting data.<sup>23</sup>

The largest randomized trial to evaluate transfusion triggers to date is in 838 intensive care patients, including those undergoing surgery.<sup>30</sup> Patients were randomized either to a restrictive transfusion strategy in which patients received transfusions to keep Hb between 7 and 9 g dl<sup>-1</sup> or a liberal strategy with Hb levels maintained between 10 and 12 g dl<sup>-1</sup>. 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.<sup>31–33</sup> Reviews have suggested laboratory evaluations of anaemia based on traditional approaches such as red cell size (mean corpuscular volume) and serum ferritin levels.<sup>34–35</sup> 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.<sup>36</sup>

## 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,<sup>37</sup> using the modified grading system adopted by the American College of Chest Physicians (Fig. 1).<sup>38</sup> 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.<sup>37–38</sup> The key studies supporting the proposed recommendations are listed and annotated in Supplementary Appendix 1. This framework provides

### Grading system

Strength of recommendation: is risk/benefit clear?

- Yes ⇒ strong recommendation=Grade 1: 'we recommend'
- No ⇒ weak recommendation=Grade 2: 'we suggest'

Quality of evidence

- High-quality evidence=A (meta-analyses, randomized controlled trials)
- Moderate-quality evidence=B (randomized controlled trials with limitations, observational studies with large effects)
- Low- or very low-quality evidence=C (observational studies, randomized controlled trials with major limitations)

Grade of recommendation=6 possible grades

- |            |            |
|------------|------------|
| ▪ Grade 1A | ▪ Grade 2A |
| ▪ Grade 1B | ▪ Grade 2B |
| ▪ Grade 1C | ▪ Grade 2C |

**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<sup>33</sup> has recommended that iron, vitamin B<sub>12</sub>, 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<sup>-1</sup>, male  $\geq 13$  g dl<sup>-1</sup>), 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,<sup>2,9</sup> 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.<sup>39</sup> 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.<sup>9</sup> As ferritin is an acute-phase reactant, traditional laboratory thresholds of  $<12$   $\mu\text{g litre}^{-1}$  may be suitable for identifying absolute iron deficiency in normal individuals, but not in patients with any evidence of an inflammatory process.<sup>36</sup> Correlation of iron stores with ferritin values has demonstrated that ferritin levels must exceed  $30$   $\mu\text{g litre}^{-1}$  to achieve a 92% sensitivity for exclusion of absolute iron deficiency.<sup>40</sup> For patients without chronic renal disease, ferritin levels  $>100$   $\mu\text{g litre}^{-1}$  confirm the presence of stored iron.<sup>9,36</sup>

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.<sup>38</sup> 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,<sup>39</sup> ongoing blood (iron) losses in excess of oral iron absorption,<sup>40</sup> and/or diminished gastrointestinal absorption of iron due to inflammation.<sup>9</sup> 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.<sup>41</sup>

## 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<sup>41 42</sup> and colorectal cancer<sup>43 44</sup> surgery. In the absence of preoperative iron supplementation, postoperative iron supplementation has not been shown to be effective.<sup>45-49</sup>

Three small series of orthopaedic surgery patients, undergoing repair of hip fracture<sup>50 51</sup> or joint replacement and back surgery,<sup>52</sup> 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.<sup>53</sup>

### 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,<sup>54-61</sup> in patients with anaemia related to cancer or chemotherapy,<sup>62-70</sup> and in patients undergoing elective surgery<sup>71</sup> 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.<sup>72</sup> A meta-analysis of 41 published studies [eight studies of ESA alone,<sup>71 73-79</sup> 22 studies of ESA augmented with preoperative autologous blood donation (PABD),<sup>39 80-100</sup> seven studies of ESA compared with PABD,<sup>71 84 101-105</sup> and four studies of ESA and other comparators]<sup>106-109</sup> 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.<sup>7</sup> 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.<sup>110</sup> ESA therapy with iron supplementation is effective in reducing subsequent need for allogeneic transfusion.<sup>72</sup>

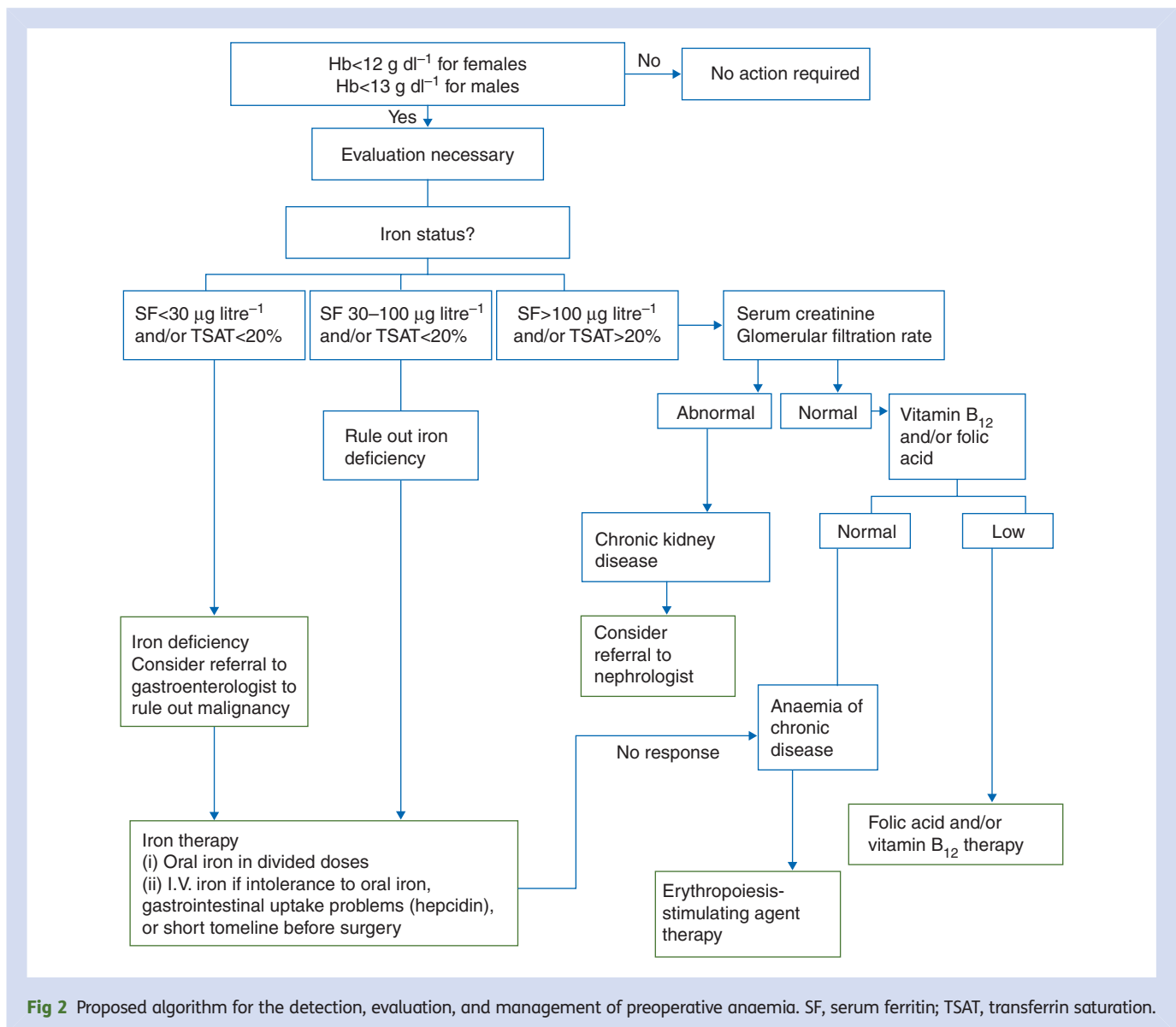
## Detection, evaluation, and management of preoperative of anaemia: an algorithm

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



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.

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## 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.

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