British Committee for Standards in Haematology Guidelines on the Identification and Management of Pre-Operative Anaemia

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Background

Anaemia is most often defined in terms of the criteria established by the World Health Organization (WHO) in 1968 (WHO 2011), namely haemoglobin (Hb) concentration of <130 g/l for men and <120 g/l for women. Pre-operative anaemia is common. Its prevalence varies from 5% to 75% depending on the population studied (Shander *et al*, 2004).

Pre-operative anaemia may significantly affect patient outcomes. Anaemia is an independently predictive risk factor for complications and death (Beattie *et al*, 2009; Spahn, 2010; Musallam *et al*, 2011). Co-existing anaemia substantially increases health care costs in medical (Ershler *et al*, 2005; Nissenson *et al*, 2005; Dowling, 2007) as well as surgical (M'Koma *et al*, 2009) patients, with substantial additional cost incurred out of hospital (Ebinger *et al*, 2004; Ershler *et al*, 2005). It further predisposes patients to requiring allogeneic blood transfusion (Shander *et al*, 2004; Beattie *et al*, 2009; Spahn, 2010; Musallam *et al*, 2011). (In this guideline, 'transfusion' may be taken to mean only allogeneic blood transfusion.) Although these relationships are associative, the body of evidence is large and consistent. The Department of Health, National Blood Transfusion Committee and National Health Service (NHS) Enhanced Recovery Partnership all consequently recommend that anaemia is investigated and treated before planned surgery, but make few recommendations on how this may be achieved (Department of Health 2007, NHS Enhanced Recovery Partnership Programme 2010, National Blood Transfusion Committee 2014).

There are three distinct reasons to consider the identification and management of pre-operative anaemia as important:

- Anaemia detected during surgical work-up may be secondary to previously undiagnosed disease, e.g. malignancy.
- To reduce the likelihood of having to resort to transfusion, thus limiting demand on donors and conserving blood supplies for those patients who need it most.
- To avoid unnecessarily exposing surgical patients to potential adverse effects of anaemia, transfusion or both.

Methods

Guideline development group

A Guideline Development Group (GDG) was commissioned by the British Committee for Standards in Haematology (BCSH), with members variously having experience in haematology, anaesthesia, surgery, critical care, gastroenterology, pre-operative assessment and transfusion medicine.

Process

This guideline was produced according to the BCSH process:

1 The GDG agrees *a priori* the methods and scope of the guideline.
2 The guideline is produced by consensus within the GDG.
3 A draft is circulated to the Transfusion Task Force (TTF) of the BCSH.
4 Following TTF approval, the draft is circulated to the BCSH Sounding Board; a group of haematologists across the UK tasked with considering the likely impact and feasibility of guideline implementation.
5 External stakeholders are identified and given the opportunity to comment. In this case, comment was received from the Association of Anaesthetists of Great Britain and Ire-

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land (AAGBI), Royal College of Anaesthetists (RCoA), Royal College of General Practitioners (RCGP), Royal College of Physicians (RCP) and Royal College of Surgeons of England (RCSEng). These comments were accounted for in the finalized guideline. The RCoA, RCGP, RCP and RCSEng subsequently endorsed the guideline.

Literature review

The Australian National Blood Authority and Australian National Health and Medical Research Council (NHMRC) published comprehensive perioperative Patient Blood Management (PBM) guidelines in 2011 (Australian National Blood Authority 2011a). These were produced after systematic review and included literature to 2009 (Australian National Blood Authority 2011b). The BCSH GDG further referred to international guidelines in surgery (Society of Thoracic Surgeons Blood Conservation Guideline Task Force *et al*, 2007, Goodnough *et al*, 2011), from the British Society for Gastroenterology (Goddard *et al*, 2011), the Renal Association(UK Renal Association 2010) and other BCSH guidelines (Ryan *et al*, 2010; Thomas *et al*, 2013).

We further reviewed the literature from 2009 to September 2014. We searched the Medline database using the Cochrane Collaboration's Highly Sensitive Search Strategy for identifying randomized controlled trials (RCTs) and search terms as detailed in Appendix S1. We also searched Embase, using a similar search strategy (Appendix S1). We included studies that evaluated a strategy for treating anaemia before surgery, and reported transfusion and/or other outcomes. Two authors independently screened the retrieved references. Additional primary literature was suggested by members.

Evidence levels and grades of recommendation

All BCSH guidelines use the evidence rating system of the GRADE working group (www.gradeworkinggroup.org).

Strength of recommendation. Strong (Grade 1): There is confidence in the balance of risk or burden versus benefit. Grade 1 recommendations may be applied to most patients.

Weak (Grade 2): The balance between benefit and burden of therapy is less clear. Grade 2 recommendations require judicious application to individual patients.

Evidence levels. Evidence quality is graded as high (A), moderate (B) or low (C).

(A) Further research is unlikely to change confidence in the estimate of effect. Current evidence derived from randomized clinical trials without important limitations.

(B) Further research may impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomized clinical trials with important limitations (e.g. inconsistent results, imprecision or potential bias), or very strong evidence from observational studies (e.g. consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Further research is likely to have an important impact on confidence in the effect estimate and is likely to change the estimate. Current evidence from observational studies, case series or expert opinion.

Clinical guideline

Relationship between anaemia, transfusion and outcome

Strong evidence indicates that pre-operative anaemia is not simply an abnormal laboratory value; it is rather an important modifiable risk factor for peri-operative morbidity and mortality.

The Australian PBM group identified 42 observational studies which consistently showed pre-operative anaemia to predict post-operative morbidity and mortality, as well as the requirement for transfusion (Australian National Blood Authority 2011a). A contemporaneous systematic review (Spahn, 2010) found similar results.

Large studies have been published since the abovementioned systematic reviews. Musallam *et al* (2011) analysed data on 227 435 surgical patients, controlling for over 60 potential confounders. Pre-operative anaemia predicted mortality and morbidity. Mild anaemia (defined as Hb >100 g/l) increased relative risk by over 30%, with there also being a relationship between anaemia severity and outcome, i.e. a 'severity-response curve'. Anaemia also strongly predicted the need for transfusion, which is again predictive of poor outcome. Ferraris and colleagues (Ferraris *et al*, 2012) analysed data and conducted propensity-matched comparisons between 15 186 patients who received one unit of donated red cells and 893 205 patients who received no blood. Transfused patients suffered more morbidity and mortality. Patients transfused >1 unit had further increased rates of morbidity and mortality, in a dose-dependent fashion. Other authors (Pedersen *et al*, 2009; Glance *et al*, 2011) made similar conclusions.

Detection of pre-operative anaemia thus helps to identify patients at risk of poor post-operative outcomes, including mortality. This is consistent with the surgical risk prediction literature. Pre-operative Hb influences risk in well-validated risk prediction models (Copeland *et al*, 1991; Whiteley *et al*, 1996; Prytherch *et al*, 2003; Richards *et al*, 2010; Smith & Tekkis, 2015). Furthermore, both iron status and Hb concentration are closely related to functional capacity (Anker *et al*, 2009), which in turn influences peri-operative risk (Hennis *et al*, 2011). Successive reports from the Royal College of Surgeons and Department of Health 2011) and National Confidential enquiry into Patient Outcome and Death (NCEPOD) (2011) recommend that the care and consent of surgical patients explicitly consider quantitative risk estimates made using predictive scores, e.g. decisions on

critical care. The effect of anaemia on mortality is thus pertinent in routine practice and will impact on Trusts' critical care resource.

Whilst anaemia is predictive of surgical risk, we could find no randomized evidence that *correction* of anaemia *alters* that risk. The exception is transfusion, where randomized evidence indicates that anaemia correction decreases transfusion requirements (Australian National Blood Authority 2011a). Given that allogeneic blood is, by definition, a limited resource, there is public health benefit to be gained from limiting its use where alternatives exist. Because previously unsuspected anaemia detected during surgical work-up may, of itself, be significant, anaemia screening also carries a health benefit beyond the planned surgical episode. The argument for screening and correction is thus strong in principle, but individualized decisions must still be made that take into account the magnitude of the proposed surgery as well as the patient's history and preferences.

Evidence summary.

- Anaemic patients are at increased risk of transfusion, mortality and major morbidity, in proportion to the severity of anaemia.

Recommendation

- **Healthcare pathways should be structured to ensure anaemia screening and correction before surgery (Grade 2B).**
- **Patients should be counselled about the relationship between anaemia, morbidity and mortality, and should be given the opportunity to defer non-urgent surgery until anaemia is investigated and treated (Grade 1C).**

Timing of assessment

We could find no research specifically into the timing of pre-operative anaemia screening and therefore considered the matter from first principles. The investigation and management of pre-operative anaemia takes time. Pre-operative preparation should ideally be a collaborative process involving primary care (Association of Anaesthetists of Great Britain and Ireland 2010). There are multiple opportunities for timely anaemia detection and management in a typical surgical pathway:

- In General Practice, when referral is considered.
- During the diagnostic pathway, e.g. when a suspicious lesion is found at endoscopy, or at a cancer multidisciplinary team (MDT) meeting.
- In the surgical clinic. Management options are then discussed at the pre-assessment visit.
- At the pre-assessment visit, with additional visits being necessary to start treatment.

If patients are only screened close to the planned operation date, there will be insufficient time to correct anaemia (Blest *et al*, 2007). Missing the above opportunities for timely diagnosis should be viewed as a failure of care processes. An agreed referral pathway that incorporates anaemia screening as part of the referral for surgery from General Practice is ideal, as this maximizes the time available for investigation and treatment. Anaemia screening, by laboratory or bedside test, is easily carried out and places minimal burden on patients. Where surgery is a likely outcome from referral, such screening is strongly advocated. In an observational study, an approach including early screening and collaboration between primary and secondary care delivered outcome improvements for patients undergoing lower limb arthroplasty (Kotze *et al*, 2012), as well as significant cost savings (Spahn *et al*, 2012).

Many surgical procedures may safely be scheduled to allow diagnosis and treatment of anaemia, and reduce risk. To do so constitutes best practice and provider organizations and commissioners may agree that referral-to-treatment time targets take account of this ('stopping the clock'). In procedures where delay presents a risk or burden to the patient, an individualized decision should be made that balances the risk of anaemia and/or transfusion against that of postponement. However, in non-urgent surgery this should only rarely be necessary if surgical pathways are properly set up. The magnitude of risk increase is proportional to anaemia severity (Musallam *et al*, 2011). Speed of response to treatment is furthermore greater in more severe anaemia, particularly in iron deficiency. Using whatever time is available before surgery to treat anaemia thus makes logical sense when surgery should be expedited.

Recommendation

- **To avoid causing unnecessary delay to patients, anaemia screening should take place when referral for surgery is first made, in order to allow investigation and correction if appropriate (Grade 1C).**
- **Where surgery is urgent, whatever time is available before operation should still be used for anaemia investigation and treatment initiation (Grade 1C).**

Diagnosis of anaemia

Anaemia may be expected as part of the presenting complaint. However, surgery represents a 'sentinel event' for many patients and work-up may reveal previously unsuspected disease. Newly diagnosed anaemic patients will therefore fall into two groups:

- Those who may safely proceed to surgery, with anaemia treatment
- Those who require investigation to exclude previously undetected serious disease.

Broadly speaking, in the surgical context anaemia may be defined as that caused by disturbances of iron metabolism (and hence potentially correctable with iron alone) and anaemia of other causes (which may require other treatments).

Anaemia related to iron metabolism. Erythropoiesis is iron-restricted if the body's absolute iron stores are insufficient (Iron Deficiency Anaemia, IDA) or if insufficient iron is available at bone marrow level in the presence of iron in the reticulo-endothelial system (Functional Iron Deficiency, FID) (Goddard *et al*, 2011; Thomas *et al*, 2013). Iron depletion may also occur without anaemia. Regenerating 10 g/l of lost blood takes approximately 165 g of stored iron in a 70 kg adult. If the serum ferritin is <100 μg/l, loss of 30 g/l Hb (1200 ml blood for a 70 kg adult) will deplete total body iron stores and precipitate IDA (Australian National Blood Authority 2011a).

The serum ferritin concentration is the most powerful test to elucidate iron status in the absence of inflammation (Goddard *et al*, 2011). In anaemia, serum Ferritin <30 μg/l is a sensitive marker of iron deficiency (Mast *et al*, 1998), with <15 μg/l being pathognomonic of IDA (Goddard *et al*, 2011). The British Society for Gastroenterology recommends specialist referral for IDA, except in pre-menopausal women, because the prevalence of cancer in unexplained IDA approaches 15% (Goddard *et al*, 2011). Given that pre-operative workup often includes a battery of tests, hypoferritinaemia without anaemia may be detected. Hypoferritinaemia (<15 μg/l) without anaemia is not sinister in young women, but is associated with a cancer prevalence of 0·9% in men and postmenopausal women and referral is indicated (Goddard *et al*, 2011). Specialist referral may also be indicated according to the severity of unexplained anaemia (e.g. men with Hb <120 g/l and women with Hb <100 g/l, or according to any locally agreed criteria) (UK Renal Association 2010, Goddard *et al*, 2011).

Ferritin is an acute phase reactant and may be elevated by inflammation or concurrent disease (Anker *et al*, 2009). Anaemia with ferritin levels below 50 μg/l or 100 μg/l is still strongly suggestive of iron deficiency in the presence of inflammation (Australian National Blood Authority 2011a, Goddard *et al*, 2011). In such circumstances, exclusion of iron deficiency may require the use of further tests (e.g. serum transferrin saturation <20%) or a therapeutic trial of parenteral iron (Australian National Blood Authority 2011a).

Anaemia not related to iron. Vitamin B12 and folate—Anaemia not related to iron disturbance may be due to other nutritional deficiencies (Vitamin B12 and folate), secondary to renal failure, or of other causes. Deficiency in vitamin B12 and folate is easily and cheaply tested for, and is recommended (UK Renal Association 2010).

Renal failure—If other common causes are excluded and the estimated Glomerular Filtration Rate (eGFR) is <30 ml/min/1·73 m^2 or <45 ml/min/1·73 m^2 in diabetics, renal failure is the likely cause. Referral should be considered if previously undetected renal failure is diagnosed as result of pre-operative screening (UK Renal Association 2010).

Inherited disorders (Ryan et al*, 2010)*—Inherited haemoglobin disorders (haemoglobinopathy) should be considered in all individuals with microcytic anaemia if there is no evidence of iron deficiency, or if red cell changes persist after adequate iron replacement. Although these conditions are more frequently associated with individuals of non-northern European origin, they are present in all ethnic groups.

Conditions most frequently associated with microcytic hypochromic indices include:

- Alpha thalassaemia
- Beta thalassaemia
- Haemoglobin E

Carriers are asymptomatic. Milder carriers may have a normal haemoglobin level with minimal reduction in mean cell volume (MCV) and mean cell haemoglobin (MCH) while others will have mild anaemia with more marked reduction in MCV and MCH. Individuals with anaemia > 20 g/l below lower limit of normal or those with symptoms or splenomegaly should be referred.

Carriers do not need haematology follow-up but their General Practitioner (GP) should be informed because the information may be important for genetic counselling. Women who have had pregnancies in recent years or partners of women with significant carrier states may have been screened as part of the national antenatal screening programme and may be aware of their haemoglobinopathy results. It is also useful to refer back to historical results, for haemoglobin, MCV and MCH, if available, as these remain relatively constant throughout adult life for a given individual; any significant deviation indicates an additional cause for anaemia.

Investigation algorithms

The Australian National Blood Authority and Network for Advancement of Transfusion Alternatives (NATA) review groups each published an investigation algorithm (Australian National Blood Authority 2011a, Goodnough *et al*, 2011). The UK context is different, particularly regarding referral-to-treatment time targets and the role of GPs in commissioning care. It is thus important that patients' GPs be involved from the outset in the management of anaemia discovered during operative work-up. GPs should include information about known anaemia in the surgical referral, so that patients are not inappropriately postponed or investigated.

It may be practicable to submit anaemic patients to a standardized battery of tests (including repeat Hb, serum ferritin, vitamin B12 and Folate), rather than engage in sequential testing. The above diagnostic considerations and initial

test results may be integrated into an investigations and referral algorithm. This writing group considers that such algorithms should be locally designed, to be implementable without disrupting surgical pathways. It should involve both primary and secondary care, and funding arrangements should be clear. The potential for gain is great, with reductions in spend on transfusion, potential reductions in length of stay, and a potential decreased burden of follow-up and treatment in primary care after discharge. Both primary and secondary care systems stand to gain from systematic pre-operative anaemia management.

Example algorithms are given in Appendix S2. These are shown with the intent of supporting organizations in creating their own systems, rather than as recommendations *per se*.

Recommendation

- **Commissioners and provider organizations should formalize integrated pathways and funding for the referral of patients found to be anaemic during surgical work-up, if the nature of the anaemia suggests that unexpected significant underlying disease is possible (Grade 1C).**
- **Patients with unexplained IDA or unexplained isolated hypoferritinaemia (serum Ferritin <15 μg/l) should be considered for further investigation and/or specialist referral (Grade 1B).**
- **In unexplained anaemia without iron deficiency, referral should be considered according to the severity of anaemia (e.g. men with Hb <120 g/l, women with Hb <100 g/l, or according to locally agreed criteria) because the likelihood of a serious cause or inherited haemoglobinopathy is proportional to anaemia severity (Grade 1B).**

Management options

The management option(s) appropriate for an anaemic patient will depend on interplay between:

- The cause and severity of anaemia
- The anticipated peri-operative blood loss (which may exceed the intra-operative loss)
- The time available between diagnosis and surgery
- Whether surgery may safely be postponed

We therefore intend that clinicians use this guideline and the results of local pathway analysis to design management algorithms for the different procedures (or procedure categories) that they perform. Integrating anaemia management with pre-existing surgical pathways is ideal.

Iron therapy

Based on 13 studies of fair to good methodological quality, the Australian PBM guidelines (Australian National Blood Authority 2011a) recommend that iron deficiency be treated pre-operatively (Grade 1B). We identified no RCTs that should alter this.

There are two options for IDA treatment: oral or intravenous iron supplementation. Oral formulations are widely available, cheap, and safe. However, oral iron is poorly bioavailable (Finch, 1994). The absorption of oral iron is variably inhibited by dietary iron chelaters (e.g. phytates and tannins) and common medications including proton pump inhibitors. Iron tablets often cause dose-related gastrointestinal side effects. Furthermore, enteral iron is poorly absorbed in the context of chronic inflammation (Weiss, 2009) or chronic renal failure, making oral iron unlikely to be effective in FID. Even with optimal absorption, the rate of haemoglobin correction is slow, typically about 10 g/l per week (Weiss, 2009). After correction of anaemia, oral iron supplementation for up to 3 months is required before iron stores are replete (Goddard *et al*, 2011). The co-administration of vitamin C supplements is recommended to enhance duodenal iron uptake (Brise & Hallberg, 1962).

Although oral iron can be as effective as intravenous iron in the medium term (Evstatiev *et al*, 2011), the intravenous route is increasingly used. Where rapid correction is desirable (e.g. cancer surgery), the parenteral route is more attractive (Beris *et al*, 2008). We identified one RCT (Kim *et al*, 2009) that compared pre-operative oral iron with parenteral iron sucrose. Target Hb attainment was more likely with parenteral iron. A single total dose infusion (ferric carboxymaltose) was furthermore found to correct anaemia quicker than iron sucrose in a small observational study (Bisbe *et al*, 2011).

Recently developed intravenous iron formulations are safer than older preparations, because the iron is encased in a carbohydrate shell (Auerbach & Macdougall, 2014). Based on all prospective reports, where high molecular weight dextrans are avoided, the serious adverse event rate is estimated at <1:200 000 administrations (Chertow *et al*, 2006; Auerbach & Macdougall, 2014). In a Cochrane review of 21 RCTs ($n = 4754$), the adverse event rate from parenteral iron was no different to that with placebo (Gurusamy *et al*, 2014). The European Medicines Agency (2013) concluded that the benefits of intravenous iron preparations outweigh their risks, provided that they are given in facilities with resuscitation equipment and that patients are observed for at least 30 min post-infusion (European Medicines Agency 2013).

The choice of iron preparation and administration route is thus not simple. It depends on interaction between agent cost, administration factors (number of visits, length of administration episode, etc.), tolerability, safety and practicability within a given surgical pathway. Organizations should take their local circumstances into account when designing their own systems.

The relative properties of parenteral iron preparations are summarized in Appendix S3.

Recommendation

- **Iron therapy is indicated in anaemic patients with absolute or functional iron deficiency (Grade 1B).**
- **Oral iron is indicated in iron deficient anaemic patients whose surgery is not urgent (Grade 1B).**
- **Iron therapy is indicated for non-anaemic patients with low iron stores (ferritin <100 μg/l and transferrin saturation <20%) scheduled to undergo surgery with predicted total peri-operative erythrocyte loss >30 g/l (>1200 ml in a 70 kg adult), to protect against post-operative iron deficiency anaemia (Grade 1C).**
- **Treatment with intravenous iron is indicated when patients are intolerant of, or unresponsive to, oral iron. (Grade 1B)**
- **Intravenous iron is indicated in functional iron deficiency or where the interval between detection of anaemia and surgery is predicted to be short. (Grade 2B).**
- **The agent chosen should take account of the surgical pathway and local circumstances. Where the time to surgery is short and/or when it is more practicable, agents that allow for single-dose treatment are appropriate. (Grade 2C).**

Vitamin B12 and folate therapy

Vitamin B12 and/or Folate deficiency may present with anaemia. These micronutrients also have other important functions and deficiency detected during the surgical preparation process should be treated (Grade 1C) (Australian National Blood Authority 2011a).

Erythropoiesis-stimulating agent (ESA) therapy

Agents available to stimulate erythropoiesis in clinical practice are all recombinant variants of the naturally occurring hormone erythropoietin, including agents such as erythropoetin alpha and darbepoetin. These agents are most commonly used in renal medicine. In addition, erythropoetin alpha is also licensed for peri-operative use, although there is no biological effect difference between different ESAs. In addition to their effects on red cell mass, ESAs may also protect against tissue ischaemia by anti-oxidative and anti-inflammatory mechanisms, and promoting small vessel angiogenesis (UK Renal Association 2010, Yoo *et al*, 2011).

The Australian review group (Australian National Blood Authority 2011a) found 11 randomized studies, all of fair to good quality, which consistently showed that ESA therapy decreased transfusion, but none were powered to provide evidence on other outcomes. A meta-analysis that partially overlaps with the above review (Alsaleh *et al*, 2013) found that ESA therapy before lower limb arthroplasty substantially reduced transfusion requirements. Where transfusion risk reduction is thought necessary, the evidence for ESA efficacy is thus strong, e.g. in patients who refuse blood, or in those with alloimmunization problems.

Much less evidence exists in support of ESA treatment to improve other patient outcomes and the literature is conflicting regarding risk-benefit balance. Concern exists that ESA therapy may worsen survival in cancer patients. A meta-analysis of 91 studies found that ESA therapy for chemo-and radiotherapy-related anaemia improves quality of life and reduces transfusion requirements, but that overall survival is worse (Tonia *et al*, 2012). In all but one (unpublished) study in this review, ESA therapy was given for >6 weeks, and for >12 weeks in 71/91 studies, making the applicability to pre-operative patients unclear. A Cochrane review also found strong evidence that peri-operative transfusion increases the likelihood of cancer recurrence after potentially curative surgery (Amato & Pescatori, 2006), so blanket advice to avoid ESAs in cancer surgery is not appropriate. A multicentre RCT powered to evaluate the safety of ESA therapy in elective spinal surgery without pharmacological thromboprophylaxis found higher rates of ultrasound-diagnosed deep vein thrombosis (Stowell *et al*, 2009). ESA therapy is expensive – USD 7300 per avoided transfusion in a recent RCT (So-Osman *et al*, 2014) – and the authors concluded that the cost was not justifiable. The clinical and cost-effectiveness of ESA therapy also falls within the scope of forthcoming guidance from the UK National Institute for Health and Clinical Excellence (2014).

ESAs thus appear effective in reducing transfusion risk, but are expensive and have potential side effects and serious complications. Individual risk-benefit decisions are necessary and further research is urgently required that evaluate the safety of ESA therapy when used peri-operatively. Consequently, we make no recommendation for the use of ESA therapy, other than where transfusion avoidance of itself is clearly beneficial to the individual, e.g. in patients who refuse blood, or those with complex alloimmunization. The UK Renal Association (2010) recommends that if used, ESA therapy be given to achieve a target Hb of no higher than 120 g/l.

The Australian PBM group (Australian National Blood Authority 2011a), Australian NATA (Goodnough *et al*, 2011) and the UK Renal Association) all recommend that iron be co-administered with an ESA in order to maximize its efficacy. We could find no evidence on the best route of iron administration to maximize ESA efficacy. Given that compliance with oral iron is often difficult and its absorption not certain (Finch, 1994; Weiss, 2009) and because ESAs are expensive, it may be pragmatic to consider the intravenous route so that therapeutic plasma iron levels are assured. Research is required before any recommendation can be made.

Recommendation

- **Where transfusion avoidance is desirable (e.g. in patients who refuse blood or those with complex alloimmunization), erythropoiesis-stimulating agent (ESA) therapy may be indicated to treat pre-operative anaemia (Grade 2B).**

- **When ESA therapy is indicated pre-operatively, it should be given with iron supplementation to maximize its efficacy (Grade 1A)**

Short-term therapy

There is emerging randomized evidence regarding very short-term management of anaemia before cardiac (Weltert *et al*, 2010; Yoo *et al*, 2011) and arthroplasty (Na *et al*, 2011) surgery. In these trials, an ESA and parenteral iron were started <1 week before surgery, without attempt to diagnose the cause of the anaemia. All three trials showed significant decreases in transfusion rate but did not report on other patient outcomes and the absolute numbers of patients involved are small. Short-term oral or parenteral iron alone proved ineffective in RCTs (Serrano-Trenas *et al*, 2011; Garrido-Martin *et al*, 2012), although there is observational evidence to the contrary (Munoz *et al*, 2014). In one small RCT ($n = 79$) in patients with intertrochanteric fracture (Kateros *et al*, 2010), ten daily ESA doses reduced transfusion requirements and accelerated Hb mass recovery. No other patient outcomes were reported.

Short-term combination therapy that includes an ESA is thus potentially efficacious, but safety and cost-effectiveness data is lacking. This GDG considers that, until better safety data is available, combination therapy should only be used after patient counselling that is explicit about the lack of safety data. We therefore make no recommendation.

Transfusion

'Top-up' transfusions have traditionally been used to prepare anaemic patients for surgery, but no randomized evidence exists that this is of benefit (Shander *et al*, 2011). Traditional practice includes pre-operative transfusion at trigger values as high was 120g/l (Karkouti *et al*, 2012), i.e. transfusion to correct pre-operative anaemia, in anticipation of future blood loss. Trials of restrictive versus liberal transfusion (for haemodynamically stable patients) showed restrictive strategies to be superior in critical illness (Hebert *et al*, 1999) and gastrointestinal bleeding (Villanueva *et al*, 2013), and safe in elderly patients after hip fracture repair (Carson *et al*, 2011). Single studies of perioperative transfusion in major cancer surgery (de Almeida *et al*, 2015) and cardiac surgery (Murphy *et al*, 2015) suggested a trigger Hb of 90 g/l may be superior to 70 g/l or 75 g/l, respectively. However, even the 'liberal' groups in the above trials were managed restrictively when compared to traditional practice (Karkouti *et al*, 2012).

Whilst the optimal transfusion threshold remains to be defined, and whilst it is probably different for different patient groups, we found no literature to support transfusion being beneficial where the target is a normal or near-normal value (i.e. transfusion given to correct anaemia). We further found no good evidence in support of pre-operative transfusion to improve surgical outcomes, and in the absence of other PBM measures, pre-emptive transfusion appears not to reduce total transfusion requirements (Karkouti *et al*, 2012).

There is thus a lack of evidence for transfusion as an effective treatment to protect against the deleterious effects of pre-operative anaemia. This should be taken in combination with the dose-dependent relationship between transfusion and complications (Ferraris *et al*, 2012), with systematic reviews showing liberal transfusion to be either inferior (Carson *et al*, 2012; Rohde *et al*, 2014) or non-beneficial (Carson & Strair, 2014; Holst *et al*, 2015) compared to restrictive strategies, and evidence of both short-term (Bolton-Maggs *et al*, 2013) and longer-term (Amato & Pescatori, 2006) risks of transfusion. Elective transfusion to normal or near-normal Hb in anticipation of operative blood loss is therefore not recommended; particularly as evidence-based anaemia treatments are available.

In situations where transfusion is likely to be unavoidable despite appropriate transfusion practice and intra-operative patient blood management (e.g. severe refractory anaemia or urgent major surgery), the question of whether pre-operative transfusion is superior to intra-operative transfusion is as yet unanswered. However, it should be emphasized that these situations are not common in non-emergent surgery if surgical pathways are properly set up.

Appendix S4 gives an overview of the management options available for pre-operative anaemia.

Limitations and future research

The main limitation of this guideline is the paucity of high-quality evidence that anaemia management improves surgical outcomes other than transfusion rates. Furthermore, there is mainly observational evidence and expert opinion for how anaemia management may be integrated into surgical pathways. These are prone to bias. Future research is required to:

- Define the clinical and health economic burden of pre-operative anaemia over the entire surgical pathway from referral to recovery
- Quantify the potential benefit for blood donors if optimal anaemia management is widely implemented
- Produce Level 1 evidence for the efficacy or otherwise of individual agents in improving surgical outcomes for patients with pre-operative anaemia
- Evaluate strategies for integrating effective treatments into programmes that are feasible for routine implementation.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

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- All attended writing group meetings to set the guideline scope, wrote the first draft section relevant to their specialty, provided critical review of guideline drafts and agreed the recommendations.
- AH co-ordinated the meetings and liaised with the BCSH Task Force and BSH Executive.
- CT reviewed the literature and selected publications for inclusion.
- AK chaired the writing group, performed the literature review, selected publications for inclusion, engaged with external stakeholders and prepared the manuscript for submission.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Literature review.

Appendix S2. Example algorithms.

Appendix S3. Relative properties of intravenous iron preparations commercially available in the UK (2014).

Appendix S4. Overview of treatment options for pre-operative anaemia.

References

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