PRODIGGEST Project

Healthcare PROtocols to improve interDIsciplinary
manaGEment of gaSTrointestinal diseases in hospital settings

ASOCIACIÓN ESPAÑOLA DE GASTROENTEROLOGÍA

REDDOCENTE Interhospitalaria
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Management of anaemia and iron deficiency in gastrointestinal bleeding

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Management of ANAEMIA AND IRON DEFICIENCY IN GASTROINTESTINAL BLEEDING

Field of application

Primary care

- **Hospital care**

Single-centre

- **Multi-centre**

Involves a single Unit or Department

- **Involves several Units or Departments**

Activity to which the protocol applies

Health promotion

Disease prevention

- **Diagnosis**
- **Treatment**

Rehabilitation

Palliative care

Professionals involved

- **Medical field**
- **Nursing**

Single specialty

- **Multiple specialties**

Contents

Management of ANAEMIA AND IRON DEFICIENCY IN GASTROINTESTINAL BLEEDING

Definition of the problem

- Acute or chronic gastrointestinal bleeding is one of the most significant problems observed by gastroenterologists, internists and surgeons.
- Upper gastrointestinal bleeding (UGIB) (bleeding from above the ligament of Treitz) is the cause of 48–160 hospital admissions per 100,000 inhabitants/year, according to the area studied, with mortality rates of 3–14% *(Miilunpohja S et al., 2017)*.
- The incidence of UGIB has decreased in the last few decades, partly due to treatment for *Helicobacter pylori* infection and the use of gastro-protection in patients requiring NSAIDs or antiplatelet (AP) drugs. The incidence of lower gastrointestinal bleeding (LGIB), however, has increased significantly in association with the ageing population, the presence of comorbidities and an increased need for anticoagulants and AP drugs *(Lanas A et al., 2017)*. The mortality rate of LGIB is around 3.3% according to the latest studies *(Oakland K et al., 2017)*.
- Mortality from acute gastrointestinal bleeding depends not only on the extent and rate of blood loss (Lanas A *et al.*, 2005), but also on the severity of the patient's comorbidities in particular.
- Rapid correction of anaemia and hypotension reduce mortality from bleeding by preventing cardiovascular decompensation, which may affect some patients *(Baradarian, Am J Gastro 2004) (Ng KS et al., 2017; Jairath V et al., 2015; Hearnshaw S et al., 2008)*.

This protocol focuses on the management and correction of anaemia and iron deficiency secondary to gastrointestinal bleeding.

Target population

- Adults who visited their local hospital with symptoms of acute (upper or lower) gastrointestinal bleeding with or without portal hypertension.
- Patients suffering with gastrointestinal bleeding during their time in hospital.
- Patients with chronic anaemia or iron deficiency secondary to faecal occult blood loss.

EXCLUSION CRITERIA

- Paediatric population.
- Patients with anaemia or iron deficiency secondary to causes other than gastrointestinal bleeding (acute or chronic), including those associated with malabsorption, inflammatory bowel disease, colon cancer, stomach cancer, chronic kidney disease, heart failure and pre- and/or peri-operative conditions[1].

[1] PRODIGGEST will develop specific protocols for these clinical conditions.

Definition of the activity to be performed

1. To review the current indications for allogeneic blood transfusion in the context of patients with acute and chronic gastrointestinal bleeding.
2. To provide guidance for achieving an adequate balance between the use and overuse of blood transfusion according to a restrictive model.
3. To develop a healthcare protocol for the management of anaemia and iron deficiency associated with acute and chronic gastrointestinal bleeding.
4. To provide information on the advantages and limitations of oral versus intravenous iron in acute or chronic gastrointestinal bleeding.
5. To provide guidelines for managing intravenous iron for safe and effective iron replacement due to gastrointestinal bleeding-associated blood loss.

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Theoretical or conceptual document

1. COMPREHENSIVE MANAGEMENT

Management of acute gastrointestinal bleeding currently requires an interdisciplinary approach with the involvement of general practitioners, emergency medicine doctors, gastroenterologists, endoscopists, surgeons, critical care practitioners, haematologists and interventional radiologists. Comprehensive clinical management of these patients includes:

- Evaluating the extent of blood loss and immediate resuscitation measures;

- Stratifying the risk based on the characteristics of the patient (age, comorbidities) and the bleeding (aetiology, quantity and/or rate of extravasation, and endoscopic warning signs of rebleeding);
- Identifying the source of bleeding (early endoscopy once the patient is haemodynamically stable);
- Treating both the cause of the bleeding and its impact (hypovolaemia, anaemia, iron deficiency and clotting disorders).

Such comprehensive management **(Table 1)** is outside the scope of this protocol. Various consensus recommendations and Clinical Practice Guidelines have been published by the *American College of Gastroenterology (Laine L et al., 2012)*, an international group of experts *(Barkun A et al., 2003 and 2010)*, the American Society for Gastrointestinal Endoscopy *(Hwang JH et al., 2012)*, the European Society of Gastrointestinal Endoscopy *(Grainek IM et al., 2015)* and the first Spanish consensus on the treatment of gastrointestinal bleeding due to peptic ulcer *(Lanas A, 2010)*, along with expert reviews *(Brandler J et al, 2017; Oakland K et al., 2017; Lu Y et al., 2014; Holster IL et al., 2011, Ng Ks et al., 2017)*.

2. TREATMENT OF ANAEMIA

PRELIMINARY CONSIDERATIONS

Gastrointestinal bleeding results in blood loss, which, in extreme cases, can lead to hypovolaemic shock and even the patient's death due to exsanguination. Therefore, allogeneic ("from another person") blood transfusion (ABT), obtained from healthy and altruistic volunteers (blood donors), has, for a long time, been considered the cornerstone of treatment for acute blood loss anaemia. However, various observational studies conducted in countries such as Spain, Portugal and the United Kingdom indicate that the use of ABT for gastrointestinal bleeding varies between 40% and 92%, which suggests significant clinical variability. This fact suggests there is a need to adapt transfusion criteria to those recommendations established in Clinical Practice Guidelines and expert reviews *(Oakland K et al., 2017; Lanas A et al., 2010; Jairath V et al., 2010, 2015; García- Erce et al., 2013; Carson JL et al., 2016; Villanueva C et al., 2013)*, without overlooking the fact that common sense and experience provide additional value when trying to find a balance between optimal and individualised use of transfusion and overuse of this resource.

Before determining what, when and who to give transfusions to, certain considerations must be highlighted:

- The initial haemoglobin (Hb) concentration of the patient suffering from gastrointestinal bleeding may not show the real extent of blood loss. Hb levels decrease as a result of haemodilution by moving fluid from the interstitial space to the vascular compartment and the infusion of intravenous fluids. Therefore, a "normal" initial Hb concentration does not rule out severe bleeding. In these cases, haemodynamic parameters (blood pressure [BP], pulse) may give a better overview of the extent of blood loss. However, overhydration may lead to a "falsely" low Hb concentration. As a result, Hb levels must be monitored regularly in the event of potentially severe bleeding disorders.

- If blood volume replacement is administered too quickly, this may cause vasodilation, the washing away of newly formed fibrin-rich haemostatic plugs and dilution of clotting factors. The impact of hypothermia on *in vivo* coagulation should also be considered. All of these factors may increase the risk of rebleeding. In the event of bleeding due to portal hypertension, overexpansion of plasma volume may also increase the risk of recurrent bleeding. A "restrictive" transfusion model is currently recommended, with emphasis on the fact that blood should not be used to increase blood volume *(Villanueva C et al., 2013; Oakland K et al., 2017)*. It is highly recommended that red blood cells be transfused one unit at a time (not two at a time), except in severe cases, and the patient should always be assessed after each transfusion *(Leal-Noval, 2013)*.

- Patients with acute gastrointestinal bleeding tend to have normocytic anaemia. The presence of microcytosis suggests the presence of chronic iron deficiency anaemia, which is generally better tolerated with a lower 30-day mortality rate *(Rockey DC et al., 2017)*.

- Identifying the source of bleeding and stopping the bleeding form part of the treatment for acute blood loss anaemia. At this point, it is essential to recognise and treat any clotting disorders that may cause bleeding to continue or to increase. In the case of gastrointestinal bleeding, thrombocytopenia is unusual and is detected in only 5.2% of patients with UGIB and in 1.3% of patients with LGIB *(Hearnshaw S et al., 2011; Oakland K et al., 2016)*. Also, INR levels >1.5 are detected in 15% and 10.6% of patients with UGIB and LGIB, respectively *(Hearnshaw S et al., 2011; Oakland et al., 2017)*, firstly because of the presence of liver failure followed by the use of oral anticoagulants (46%) *(Hearnshaw S et al., 2011)*, and secondly because of the use of warfarin (73%) *(Oakland et al., 2017)*. The United Kingdom's National Institute for Health and Care Excellence (NICE) recommends offering platelet transfusions to patients who have significant bleeding and a platelet count <30 x 10^9 *(NICE, 2015)*. Moreover, the recommendation for reversing anticoagulation due to the effect of oral anticoagulants is to use prothrombin complex concentrates and vitamin K *(Hunt et al., 2015)*, the application of which has decreased the need for fresh frozen plasma (FFP) transfusions to <1% in the United Kingdom in patients with LGIB taking warfarin *(Oakland K et al., 2016)*.

One point that was a cause of controversy some decades ago was the recommendation to not use endoscopic procedures in the presence of coagulopathy. Today, however, this is considered a mistake and the presence of mild or moderatebleeding disorders hemostatic disorders is not considered a formal contraindication for diagnostic endoscopies *(Wolf AT, 2007)*. Nevertheless, in patients with INR >3, some authors recommend adjusting their INR to <3 prior to performing an endoscopy. In the past, this was achieved by administering FFP. However, the high volume of FFP required, its reduced effectiveness and the time needed to thaw and administer the FFP has resulted in recommendations to administer prothrombin complex concentrates *(Leal 2013, García- Erce)*, especially if signs of risk of rebleeding (*jet* arterial bleeding or the presence of a visible vessel) are identified during the procedure or if endoscopic haemostasis procedures were performed when INR was still >1.5.

- Finally, an ABT will be given, as prescribed by a doctor, and, if possible, after the corresponding informed consent form has been signed and potential alternatives have been offered. We must not forget that blood is an expensive commodity (€350 per unit), depends on the altruism of donors and is not exempt from adverse effects **(Table 2)**.

MANAGEMENT OF ANEMA DUE TO ACUTE BLOOD LOSS

The decision as to what, who and when to give a transfusion depends on the patient's condition. We will use the strategy known as PBM (*Patient Blood Management*) **(Figure 1)**, which uses the following criteria:

Extent of bleeding (impact on haemodynamic stability)

The presence of dyspnoea, chest pain, tachycardia, hypotension refractory to initial blood volume replacement, obnubilation and oliguria are warning signs or symptoms.

Data provided by the medical history

It is necessary to record and consider all the variables that may have an influence on the decision to administer a red blood cell transfusion (and the rate of transfusion) and the decision regarding the route of administration of iron replacement therapy (oral *vs.* intravenous), including:

- Cardiopulmonary disease
- Recent history of ischaemic or thrombotic events
- Chronic kidney disease
- Imminent surgery (<30 days)
- Any clinical condition that may interfere with oral iron availability or absorption

Lab tests: the minimum test requirements include

- Red blood cell counts
- Red cell distribution width (RDW)[1]
- Mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH)
- Reticulocyte count
- Blood cell differential count (formula) (optional)
- Serum ferritin, transferrin saturation (TS)[2]
- CRP concentration[3]
- Creatinine and urea

[1]RDW (Red cell distribution width): parameter that appears on standard full blood counts and that refers to the variation in red blood cell size: it is expressed as the ratio between the coefficient of variation of red blood distribution width divided by the mean corpuscular volume (MCV), expressed as a percentage. RDW = (standard deviation of MCV ÷ mean of MCV) x 100.7.
The normal reference interval for RDW of human red blood cells varies between 10.6% and 14.7% and is elevated in iron deficiency anaemia.

[2]In the context of acute bleeding, ferritin levels and TS do not allow iron deficiency to be estimated.

[3]The CRP value in the context of acute bleeding is relative. If the patient has a known inflammatory condition, it may help interpret ferritin levels properly.

More extensive tests include (according to the clinical scenario):

- Serum vitamin B12 and folic acid concentrations
- Haptoglobin
- Soluble transferrin receptor (sTfR)
- Percentage of hypochromic red blood cells
- Reticulocyte haemoglobin
- Mean reticulocyte volume
- Percentage of microcytic red blood cells
- Lactate dehydrogenase (LDH)
- Percentage of hypochromic red blood cells
- Reticulocyte haemoglobin

Complementary tests

- An endoscopy of the gastrointestinal tract (upper or lower, as required) or, in its absence, the results of a CT angiogram (in the presence of severe haemodynamic instability) allow not only the cause of the bleeding but also the activity of the bleeding to be identified; an endoscopy also allows the presence of warning signs of rebleeding to be detected according to the Forrest Classification System. In the latter case, an endoscopy reduces the risk of rebleeding and, therefore, also the risk of transfusion.

Red blood cell transfusion (PBM strategy)

The PBM (Patient Blood Management) strategy is a global initiative to reduce the rate of avoidable or inappropriate transfusions recommended by various international organisations, including the United Kingdom's National Blood Transfusion Committee, the National Institute for Health and Care Excellence *(NICE, 2015)* and the Cochrane Database *(Carson JL et al., 2016)*. In the United Kingdom, for example, 43% of patients admitted to hospital with upper gastrointestinal bleeding receive an ABT, while 26% of patients with lower gastrointestinal bleeding receive such a transfusion *(Hearnshaw et al., 2011; Oakland et al., 2017)*. Many of these transfusions are performed with no clinically significant anaemia (Hb ≥80 g/L: 41.4% in patients with UGIB and 60% in LGIB) *(Hearnshaw S et al., 2011; Oakland et al., 2017)*.

Measures used to avoid transfusions proposed by the PBM strategy include:

MEASURES FOR AVOIDING TRANSFUSION PROPOSED BY THE PBM STRATEGY

- Intravenous iron replacement therapy (see indications)
- Strategies to reduce the risk of bleeding associated with invasive procedures
- Limiting the transfusion volume as much as possible when feasible
- Study of anemia and specific treatment of it
- Reversal of anticoagulant and antiplatelet drugs
- Study and treatment of coagulopathy

The results of various studies conducted support the application of restrictive transfusion threshold, not only to reduce the number of unnecessary transfusions, but also to reduce the rate of rebleeding, morbidity and even mortality *(Villanueva C, 2013; Jairath V, 2010, 2015; Gralnek IM, 2015)*. Application of these restrictive criteria results in benefits, not only in terms of reduced transfusion-associated risks, but also in terms of cost savings *(Goodnough & Murphy, 2014; Goodnough LT, 2017)*. In the United Kingdom alone, the National Health Service (NHS) saved £3.3 m in one year as a result of this restrictive policy on blood transfusions for LGIB *(Jairath et al., 2015)*. **Tables 3 and 4** show common anaemia assessment and transfusion errors.

The following table summarises the factors that influence the decision to give transfusions.

VARIABLES THAT INFLUENCE THE DECISION TO GIVE RED BLOOD CELL TRANSFUSIONS TO PATIENTS WITH ACUTE GASTROINTESTINAL BLEEDING

1. Bleeding-dependent variables

Nature, source, extent and activity of bleeding at the time of assessment (e.g. overexpansion of plasma volume increases the risk of rebleeding in patients with gastro-oesophageal varices).

2. Impact of bleeding on the patient's haemodynamic stability

The following are considered warning signs or symptoms (WS): dyspnoea, precordial pain, orthostatic hypotension and tachycardia.

3. Likelihood of rebleeding

Especially the presence of endoscopic signs of risk, such as active bleeding at the time of the endoscopy or identification of a visible vessel.

4. Comorbidities that increase the risk of severe or persistent bleeding (including administration of anticoagulants or anti-platelet drugs)

5. Associated pathologies that increase the risk of complications:

- Diabetes
- Hypertension
- Arrhythmia
- COPD
- Ischaemic heart disease
- Heart failure
- Cerebrovascular accidents
- Organ dysfunction (OD) (heart, brain, kidney, lung or liver)

According to these factors and PBM (Patient Blood Management) policies, the following recommendations have been established.

1. Haemoglobin <7 g/dL (70 g/L)

This is considered the cut-off point for deciding whether to give a transfusion when there are no risk factors, warning signs or organ dysfunction. The figure is indicative. In patients with no comorbidities, no symptoms and with inactive bleeding and a low risk of rebleeding, expectant management may be possible with no transfusion.

2. Haemoglobin <8 g/dL (80 g/L)

Only consider ABT in those patients with risk factors, essentially in the presence of ischaemic heart disease, heart failure, severe arrhythmia, COPD or other conditions that increase the risk of vascular events (diabetes, hypertension). In these cases, the recommendation is to keep Hb levels above 80 g/L and at around 90 g/L.

3. Haemoglobin <9 g/dL (90 g/L)

Only consider ABT in the presence of organ dysfunction (heart, brain, lung or liver).

You must remember that "common sense" should always prevail and actually determines the balance between use and overuse of transfusion regardless of lab test results.

- Furthermore, PBM (Patient Blood Management) policies recommend single-unit red blood cell transfusions ("one unit at a time"), followed by reassessment (NICE 2015). The Spanish Ministry of Health, in its "COMMITMENT TO THE QUALITY OF THE SCIENTIFIC SOCIETIES IN SPAIN" document, highlights

the following recommendations of the *Sociedad Española de Hematología y Hemoterapia* [Spanish Society of Haematology and Haemotherapy]:

- "Do not transfuse more units of red blood cells than is necessary to relieve symptoms of anaemia or to restore a patient to a safe haemoglobin range (7 to 8 g/dL in stable, non-cardiac patients)".
- "Do not give red blood cell transfusions in the case of iron deficiency anaemia unless haemodynamically unstable".

CUT-OFF POINTS FOR TRANSFUSIONS IN PATIENTS WITH CHRONIC ANAEMIA SECONDARY TO OCCULT BLOOD LOSS

The cut-off point for Hb concentrations in the case of chronic iron deficiency anaemia, according to the Recommendations of the Sociedad Española de Transfusión Sanguínea [Spanish Society for Blood Transfusion] **(4th edition, 2015)**, is different from that observed in the case of acute bleeding.

- Haemoglobin <5 g/dL (50 g/L): consider ABT.
- Haemoglobin <6 g/dL (60 g/L): consider ABT in the presence of warning signs and symptoms (dyspnoea, precordial pain, tachycardia, orthostatic hypotension).
- Haemoglobin <7 g/dL (70 g/L): consider ABT in the presence of risk factors (cardiopulmonary failure, ischaemic heart disease).
- Haemoglobin <8 g/dL (80 g/L): observation and correction of iron deficiency.

Figure 2 shows the indications for transfusion in patients with acute gastrointestinal bleeding in the form of an algorithm; **Figure 3** shows the indications for transfusion in patients with chronic anaemia associated with occult gastrointestinal bleeding (see Operational documents section). **Figure 4** shows the number of units of red blood cells saved at Hospital San Jorge (Huesca) as a result of applying this restrictive policy led by the Transfusion Unit of the Haematology and Haemotherapy Department.

TREATMENT OF IRON DEFICIENCY

Preliminary considerations

- After suffering from acute gastrointestinal bleeding, a reduction in red blood cell volume and the urgent need for subsequent cell regeneration lead to iron deficiency (ID), which must be corrected to avoid iron deficiency anaemia (IDA).
- A Spanish study showed that more than 60% of patients have iron deficiency anaemia within a month of non-variceal UGIB *(Planella M et al., 2015)*. The study identified the following risk factors for the development of ID: patients aged >75, elevated uremic concentrations at admission (>80 mg/dL), initial ferritinemia <65 µg/L, initial Hb levels <100 g/L and transferrin saturation <10% at day 5. In view of these results, iron replacement therapy should start as soon as anaemia or ID is detected in order to replace the lost red blood cell volume as soon as possible. There are some excellent reviews on the metabolism and pathophysiology of ID *(Muñoz M et al., 2009, 2011)*.

- To summarise, iron is crucial, not only due to its involvement in erythropoiesis and oxygen transport, but also due to its decisive role in energy production, maturation of the immune system and efficient functioning of the body's organs *(Wessling-Resnick M, 2010; Wang J 2011; Ghosh K, 2006; Montoro M, 2016)*.
- Unfortunately, the terms ID and ID anaemia are often used interchangeably by doctors when they are not always synonymous *(World Health Organization, 2001)*. Therefore, according to the definition given by an International Committee of experts, ID is understood to be a health-related condition in which iron availability is insufficient to meet the body's metabolic needs and which can be present with or without anaemia *(Capellini MD et al., 2017)*.
- An important point is that ID itself is responsible for certain symptoms, even in the absence of anaemia, including fatigue, weakness, poor exercise tolerance and lack of concentration, which, although responsible for a major impact on health-related quality of life, are often only recognised once iron stores have been replenished *(Koduru P, 2016; Comin-Colet J et al., 2013; Gasche C et al., 2007; Wells C et al., 2006; Finkelstein FO, 2009)*. Parameters leading to the diagnosis of anaemia and ID are summarised in **Table 5**. **Table 6** shows a group of gastrointestinal diseases that may lead to the onset of ID and IDA.

Oral iron *versus* intravenous iron

The choice between oral iron and intravenous iron depends on various factors, such as severity and speed of onset of anaemia, costs, availability of existing formulations, patient's tolerance of oral iron replacement therapy and the existence of limiting factors (e.g. malabsorption of oral iron, allergies to intravenous iron).

Under suitable conditions, administration of oral iron is effective, readily available, cheap and safe, although up to 70% of patients treated with oral iron (especially iron sulphate) report gastrointestinal side effects *(Tolkien Z et al., 2015)*. **Table 7** shows several considerations to be taken into account for oral iron replacement therapy *(Auerbach M et al., 2016; Schrier SL, 2015; Rimon E et al., 2005)*.

Intravenous (i.v.) iron compounds are safe, provide the total dose required, quickly increase Hb levels, promote more effective replenishment of iron stores and lower rates of adverse effects (lower does not mean none) and lower rates of drop-out from treatment (better adherence) *(Leal-Noval SR et al., 2013; Ferrer-Barceló L et al., 2016; Koduru P, 2016; Salvadori U, 2016)*.

Table 8 summarises the advantages and disadvantages of oral iron versus intravenous iron.

Indications for intravenous iron in gastrointestinal bleeding

WHILE IN HOSPITAL

- Need for rapid correction of anaemia (moderate-severe anaemia)
- Concomitant inflammatory status (CRP >5 mg/dL) (< efficient absorption of oral iron due to the effects of hepcidin on ferroportin)
- In patients with gastrointestinal bleeding who also meet any of the following conditions:
  - Facing imminent surgery (<30 days) with estimated peri-operative blood loss >1–1.5 l (e.g. when bleeding is due to a

resectable malignancy or the patient is admitted while waiting for an orthopaedic hip surgery)

- Need for invasive surgery with a risk of significant bleeding
- Need for erythropoiesis-stimulating agents (e.g. EPO for chronic kidney disease) in order to prevent the primary cause of non-response to EPO, which is **functional iron deficiency** (situation in which iron requirements exceed iron stores available at that time). The term *functional iron deficiency* implies iron status with ferritin <100 µg/dL and transferrin saturation <20% (ferritin <500 µg/L and TS <30% in the presence of chronic kidney failure)

- Need for artificial feeding (parenteral or enteral)
- As a possible alternative to ABT when this is not accepted

AFTER HOSPITAL DISCHARGE

In the event of oral iron failure due to:

- Non-adherence
- Side effects that do not respond to recommended measures for improving tolerability **Table 7**
- Monthly increments <1 g/dL (iron deficiency anemia which does not respond to oral iron)[1]

Reasons that may explain refractoriness include:

- Interference with absorption (hypoacidity secondary to chronic autoimmune atrophic gastritis or the use of proton pump inhibitors, lymphocytic duodenosis due to *H. pylori* infection)
- Reduced surface area available for absorption (gastrectomy, bariatric surgery)
- Gluten-sensitive enteropathy or other clinical conditions that cause malabsorption, including oedematous bowel loops due to heart or chronic kidney disease or severe hypoalbuminaemia
- Active inflammatory bowel disease. Consider other inflammatory conditions such as systolic heart failure, left ventricular ejection fraction (LVEF) <45%

1 Intravenous iron replacement therapy must be considered prior to discharge if the doctor is aware of such factors that limit absorption while still in hospital.

Iron deficiency anaemia associated with chronic faecal occult blood loss

These patients may be treated with oral iron formulations, except for in those situations described in the section on *Oral iron versus intravenous iron* (page 14). In the event of side effects, it may be possible to change formulation, administer oral iron after meals (reduces absorption but improves tolerance), limit doses to a maximum of 100 mg/day or divide the total daily dosage into 2 doses, which may be useful in some cases. Some authors recommend trying at least three different formulations before considering the use of intravenous iron in the event of side effects due to oral iron usage *(Beneitez D, 2017)*, although there are no studies with good methodological designs to support this recommendation.

Intravenous (i.v.) iron dose calculation

The Ganzoni formula has classically been used to calculate the amount of iron to be administered. This formula is based on body weight, actual Hb compared to target Hb and iron stores. However, this formula underestimates the iron dose in cases of acute bleeding. Also, the formula is only reliable in cases of pure iron deficiency, not in cases of mixed anaemia where anaemia may be partly due to other causes, which may lead to excessive iron replenishment with subsequent overload.

Figure 5 shows an algorithm that pragmatically calculates intravenous iron replacement based on weight and Hb levels. Today, this is the easiest, quickest and most efficient method and is, in fact, the method that is most commonly used in hospital settings in the context of bleeding, especially in severe cases.

On the whole, administration of 200 mg of intravenous iron results in an increase in Hb that is equivalent to the increase observed with 1 unit of red blood cells.

SIMPLE DOSE CALCULATION FOR ADMINISTRATION OF i.v. IRON BASED ON WEIGHT AND HAEMOGLOBIN

	Weight 35–70 kg	Weight ≥70 kg
Hb ≥10 g/dL	1,000 mg (single dose)	1,500 mg (two doses: 1,000 + 500 mg)
Hb <10 g/dL	1,500 mg (two doses: 1,000 + 500 mg)	2,000 mg (two doses: 1,000 + 1,000 mg)

GANZONI FORMULA

Total iron deficit (mg) =
Body weight (kg) x (Target Hb[1] - Actual Hb) [g/dL] x 2.4[2]
+
iron stores (mg)[3]

[1] 13 g/dL for a body weight of less than 35 kg and 15 g/dL for a body weight of more than 35 kg
[2] Factor 2.4 = 0.0034 x 0.07 x 10,000; where:
0.0034: iron content of haemoglobin (0.34%);
0.07: blood volume 70 ml/kg of body weight = 7% of body weight;
10,000: conversion factor 1 g/dL = 1,000 mg/L.
[3] 500 mg if the body weight is greater than 35 kg or 15 mg/kg if the body weight is less than 35 kg.

Exclusion criteria for administration of i.v. iron

- Active uncontrolled bleeding (until haemostasis is achieved)
- Haemodynamic instability: systolic blood pressure <90 mmHg or heart rate >100 bpm[1]

[1]Only give transfusions until the patient is haemodynamically stable.

- Uncontrolled hypertension (hypertensive emergency/urgency)
- Contraindications for administration of i.v. iron:
  - Persistent bacteraemia
  - History of asthma or severe eczema, serious known allergy or hypersensitivity to other parenteral iron-containing products
  - Transferrin saturation (TS) >25% or ferritin >300 µg/L with TS >25% (in inflammatory conditions)
  - Haemochromatosis/haemosiderosis/porphyria cutanea tarda
  - 1st trimester of pregnancy or breastfeeding*

[Safety data are available for ferric carboxymaltose during breastfeeding, with breast milk iron levels <1% documented].

Location of the patient at the time of i.v. iron administration

PATIENT WHOSE CLINICAL CONDITION REQUIRES HOSPITAL ADMISSION DUE TO THE NATURE OF THE BLEEDING OR THE PRESENCE OF COMORBIDITIES PRONE TO DECOMPENSATION

- General hospital ward or ICU, as applicable
- Always once the patient is haemodynamically stable
- According to pharmacovigilance and haemovigilance guidelines, it is recommended to avoid simultaneous iron and red blood cell transfusions since, in the event of serious adverse effects, it is impossible to discern which component has caused the reaction

PATIENT SEEN IN THE EMERGENCY ROOM

- If risk stratification (Rockall risk score) indicates that the patient can be discharged, i.v. iron may be administered in the A&E department before discharging the patient
- If the patient cannot be discharged, on the ward or in the ICU

PATIENT SEEN IN THE OUTPATIENTS DEPARTMENT

- Day clinic

Characteristics of intravenous irons in Spain

Spain essentially has 4 iron preparations for intravenous administration. **Table 9** shows the brand name, active ingredient, indications, maximum iron dose as an infusion, time over which the maximum infusion dose is administered, maximum iron dose as an injection,

number of hospital visits for administration of 1,000 mg and use in children and adolescents.

Adverse effects associated with i.v. iron infusion

Adverse effects associated with iron infusion are really uncommon. The most common include:

- Nausea
- Headache
- Dizziness
- Hypertension
- Skin rash
- Injection site reactions
- Hypophosphataemia
- Increase in ALT levels
- Hypersensitivity reactions (anaphylactoid reaction: rare)*

* An adverse reaction is considered rare when its frequency is 0.01–0.001%. Table 10 summarises the recommendations of the Spanish Agency of Medicines and Medical Devices in relation to the onset of potentially serious hypersensitivity reactions during or after the injection of intravenous iron.

Nursing information sheet

- Look into any history of drug allergies, asthma or severe eczema
- Ask about the possibility of pregnancy
- Tell the patient to report any discomfort or reaction experienced during the infusion
- Administer as an intravenous infusion as prescribed
- Record vital signs before and at the end of infusion (BP, heart rate [HR] and temperature)
- Inform the medical team of any complication, adverse reaction or relevant change in vital signs
- After the infusion, monitor the patient for 30 minutes (symptoms/signs of hypersensitivity, adverse effects)
- Have adrenaline (0.5 ml), hydrocortisone (200 mg), methylprednisolone (1 mg/kg) and atropine (1 ampoule) on hand for rapid administration, if required

* Administration of dexchlorpheniramine is not recommended since it may aggravate the reaction.

Actions to be taken in the event of adverse effects

MILD

- Discontinue the infusion until all symptoms disappear
- Restart the infusion at a slower rate (slower infusion rate)

MODERATE

- Discontinue the infusion
- Administer 1 mg/kg of intravenous methylprednisolone
- Monitor the patient for 4 hours or until all symptoms disappear

SEVERE

- Administer 1,000 ml of saline solution, oxygen (if required), 0.5 mg of intramuscular adrenaline and 200 mg of intravenous hydrocortisone and admit to hospital if necessary.

Summary and conclusions

- Gastrointestinal bleeding is common in hospital settings and requires an interdisciplinary team approach. Blood volume depletion, loss of red cells mass and associated clotting disorders require support and replacement strategies that must be agreed upon with the Haematology Department and the Transfusion Committee.
- The decision to give a transfusion of red blood cells is challenging and must be made on an individual basis according to the source, activity and extent of bleeding and the patient's comorbidities.
- The decision of whether to administer oral or intravenous iron in a patient with bleeding will depend on multiple factors, including the severity of anaemia, presence of inflammation, costs and adherence to treatment with oral iron.

Operational documents

TABLE 1. COMPREHENSIVE MANAGEMENT OF GASTROINTESTINAL BLEEDING

Essential data from the medical history
Ask about the use of NSAIDs, aspirin®, anticoagulants or antiplatelet agents.
Ask about alcohol consumption, history of previous bleeding episodes, previous known or suspected chronic liver disease or bleeding disorder.
Special attention to any comorbidity with a risk of decompensation due to blood volume depletion (COPD, coronary or chronic heart failure, chronic kidney disease).
Essential data from the physical examination
Taking the patient's vital signs (HR, BP), as well as the patient's skin colour and temperature and recording the oxygen saturation levels make it possible to estimate the extent of bleeding and its potential repercussions on homeostasis and haemodynamic stability.
A rectal examination provides useful information for establishing the potential source of bleeding (melaena, haematochezia, etc.).
Diagnostic tests
Haemoglobin levels (initially normal levels may not be representative in the context of severe bleeding), platelet count, coagulation tests (prothrombin time, INR, aPTT and fibrinogen), liver enzymes (AST/ALT), albumin, blood urea nitrogen (BUN) and creatinine.
ECG and cardiac enzyme tests in patients at risk of coronary event (elderly patients, history of ischaemic heart disease or presence of symptoms suggestive of myocardial hypoxia: chest pain or dyspnoea).
Investigate the source and nature of the bleeding once the patient is haemodynamically stable (early endoscopy). If the patient is not haemodynamically stable, choose alternative diagnostic studies (CT angiography).

Management of ANAEMIA AND IRON DEFICIENCY IN GASTROINTESTINAL BLEEDING

Risk stratification using validated scores (*Rockall and Glasgow-Blatchford score*).

Treatment

Make sure the airway is clear and closely monitor the patient's vital signs, heart rate, urine output and O2 saturation levels.

Prevent the patient from eating or drinking anything - "nil by mouth".

Insert two peripheral venous cannulae (14–16 gauge). In patients who are severely and persistently haemodynamically unstable, it may be necessary to insert a catheter into the pulmonary artery.

Fit a nasal oxygen cannula, especially in the event of severe bleeding or comorbidities that may compromise myocardial or cerebral oxygenation.

Treat hypotension initially by rapid infusion of crystalloid solutions.

Consider "restrictive" transfusion of red blood cells (one unit at a time) under the following circumstances:

- The patient is haemodynamically unstable despite the administration of crystalloid solutions.
- Haemoglobin <9 g/dL (90 g/L) in the presence of organ dysfunction (heart, brain, lung or liver).
- Haemoglobin <8 g/dL (80 g/L) with risk factors, essentially in the presence of ischaemic heart disease, heart failure, severe arrhythmia, COPD, etc.
- Haemoglobin <7 g/dL (70 g/L) in low-risk patients.
- Avoid overexpansion of plasma volume in patients with oesophageal varices.

Identify and correct any factor that may affect blood clotting according to established recommendations.

Consider i.v. iron in appropriate situations (see protocol).

Contact the gastroenterologist (endoscopist) and, in severe cases, assess the involvement of other specialists (surgeons, anaesthetists, interventional radiologists).

Drug treatment

- Proton pump inhibitors in patients with gastroduodenal peptic ulcer, Mallory-Weiss syndrome or reflux oesophagitis.
- Drugs with vasoconstrictive effects on the splanchnic arterial circulation (somatostatin, glypressin) if gastrointestinal bleeding due to portal hypertension is suspected or diagnosed.
- Antibiotics (ceftriaxone, fluoroquinolones) in patients with liver cirrhosis.

Endoscopic treatment

- Transendoscopic haemostasis in patients with upper (peptic or Dieulafoy's lesion) or lower gastrointestinal bleeding (diverticula, angiodysplasia).
- Banding (or sclerotherapy) in oesophageal varices.

Radiological treatment

- Transcatheter embolisation in select cases, TIPS in gastrointestinal bleeding due to portal hypertension that does not respond to conservative treatment with drugs that have vasoconstrictive effects on the splanchnic arterial circulation, endoscopic treatment or hepatic venous pressure gradient that is predictive of conservative treatment failure.

Surgical treatment (in the event of failed conservative procedures).

TABLE 2. ACUTE TRANSFUSION REACTIONS

Immunological reactions
Acute haemolytic transfusion reaction (AHTR) (1/6,000).
Febrile non-haemolytic transfusion reaction (1/300).
Cutaneous allergic transfusion reactions and urticaria (1/50–100).
Anaphylactic reaction (1/20,000–50,000).
Acute non-cardiogenic pulmonary oedema: transfusion-related acute lung injury (TRALI) (1/1,000–5,000).
Fatal haemolysis (1/1,000,000).
Non-immunological reactions
Bacterial contamination (1/5,000,000).
Transfusion-associated circulatory overload (TACO) (1/100–500).
Hypotension.
Non-immunological haemolysis.
Others: hypocalcaemia, hyperkalaemia (cardiac arrest), hypothermia, hyperglycaemia, etc.

DELAYED TRANSFUSION REACTIONS

Immunological reactions
Delayed haemolytic transfusion reaction.
Alloimmunisation against cell antigens (also against platelets and leukocytes) (1/5–100).
Graft-versus-host disease (GvHD).
Transfusion-related immunomodulation (TRIM).
Post-transfusion purpura.
Non-immunological reactions
Transfusion-transmitted infections (*): virus (Hepatitis A, B, C, E, HIV 1-2, West Nile virus, HTLV I-II, Cytomegalovirus, Herpesviridae viruses, TTV, SEN-1, SARS, etc.), protozoa (malaria, babesiosis, Chagas disease, etc.), prion (new variant of Creutzfeldt-Jakob disease).
Transfusional haemosiderosis (iron overload).

(*): Malaria 1/4,000,000; HIV <1/2,000,000; HCV <1/1,000,000; HTLV: 1/641,000; HBV: 1/100,000.

TABLE 3. ANAEMIA ASSESSMENT, COMMON MISTAKES

Overestimating Hb levels
Normally, "anaemia" is only considered to be present when Hb levels are below 11 g/dL (in elderly patients), 12 g/dL (in women of child-bearing potential) or 13 g/dL in men, but it is often forgotten that such values are estimated at sea level (they should be increased by almost 1 point per 1,000 metres) and intra-individual variation is often ignored. For example, if Hb levels decrease by more than 2 g/L, anaemia should be suspected.
Inappropriate timing of anaemia tests
Anaemia lab tests are often requested once the patient has received a transfusion, which alters analytical values ("we are studying the transfusion"). Most laboratories keep serum samples for up to one week and, therefore, in the above situation, it may be possible to request *a posteriori* testing of the pre-transfusion sample.
Assuming that the patient's anaemia is only iron deficiency
We often only consider iron deficiency anaemia and forget to request tests for inflammatory markers (C-reactive protein [CRP] and haptoglobin), B12 and folic acid levels and iron metabolism. This makes it harder to correctly identify other types of anaemia of inflammatory, deficiency or mixed origin.
Assuming that all cases of iron deficiency anaemia are microcytic
It is often assumed that all cases of iron deficiency anaemia are microcytic and that all cases of B12 deficiency anaemia are macrocytic. This is only true in a very small number of cases of chronic, long-term unifactorial anaemia, but not in cases of mixed anaemia, in elderly patients (it is not uncommon for anaemia to be normocytic, especially in elderly patients) or in rapid onset anaemia (very often normocytic). In post-bleeding or haemorrhagic anaemia, accompanying reticulocytosis can also cause false macrocytosis.

TABLE 4. COMMON BLOOD TRANSFUSION MISTAKES

Systematically transfusing "two units at a time"
ABT should not be administered "two units at a time"; instead the minimum quantity required to reverse or prevent symptoms or signs of hypoxia should be administered. It must be remembered that the volume of red blood cells is not homogeneous and their Hb content varies from less than 40 to 60 g per unit, regardless of the weight or anthropomorphic characteristics of the patient. Many patients are likely to only need a "single unit" of red blood cells.
Performing mandatory cross-matching and reserving of blood units
Pre-transfusion testing includes blood typing, Rh typing and irregular antibody screening tests. Cross-matching and reserving of blood units is not mandatory as this depends on the practices and policies of the transfusion service. Pre-transfusion test samples are valid for a minimum of 72 hours.
Systematically administering premedication
Despite usual clinical practice, there is no justification or evidence for universal administration of premedication or routine post-transfusion administration of diuretics. Such practices in fact may cause more side effects. However, always check the recipient's blood type and identity before starting any transfusion.

TABLE 5. CRITERIA FOR DIAGNOSING IRON DEFICIENCY

Ferritin (acute-phase reactant) <30–100 µg/L*.
(*) Since ferritin is an acute-phase reactant, levels <100 µg/L may be indicative of iron deficiency in the presence of inflammation.
Transferrin (>300–350 mg/dL).
Transferrin saturation <20%.
MCV (<81 fl).
MCH (<28 pg).
RDW (>15%).
Other indicators of iron deficiency
Hypochromic red blood cells (>5%).
Soluble transferrin receptor (sTfR) >2.0.
sTfR/log ferritin index.
Reticulocyte haemoglobin <27 pg.
Reticulocyte haemoglobin content (rMCH).
Low haemoglobin density (LHD %) >5–10%.

TABLE 6. GASTROINTESTINAL CAUSES OF ID AND IDA

Lesions causing gastrointestinal bleeding (macro or microscopic)
Gastroduodenal peptic ulcer.
Angiodysplasia.
Inflammatory bowel disease.
Aspirin® or non-steroidal anti-inflammatory drugs.
Gastrointestinal malignancies.
Diverticular bleeding.
Post-operative bleeding.
Large hiatus hernias (Cameron lesions).
Parasite infections.
Impaired absorption due to limited availability of or damage to enterocytes
Low-iron diets.
Chronic autoimmune atrophic gastritis.
Coeliac disease/non-coeliac gluten sensitivity.
Inflammatory bowel disease.
Intestinal lymphoma.
Bariatric surgery/gastric bypass surgery.
Short bowel syndrome.
Gastrectomy or gastrojejunostomy.
Bacterial overgrowth.

TABLE 7. ADVANTAGES AND LIMITATIONS OF ORAL OR INTRAVENOUS IRON REPLACEMENT THERAPY

	Advantages	Limitations
Oral iron	• At the right dose, it is effective in many patients. • The risk of serious adverse effects is practically non-existent. • The cost is very low.	• Gastrointestinal side effects are common. • Adherence may be low. • Unsuitable for iron replacement in cases of severe bleeding or continuous occult blood loss. • Replenishment of iron stores may take several months. • Total costs may be high when absenteeism and presenteeism costs are combined.
Intravenous iron	• It is effective in most cases. • Faster correction of anaemia and its symptoms. • Possibility of administering high doses (up to 1,000 mg of elemental iron) in a single infusion. • Adherence is guaranteed. • No gastrointestinal side effects.	• Intravenous infusion requires monitoring. • Although uncommon, infusion-related reactions and allergies have been reported. • Special equipment and trained staff are required to treat potential infusion-related reactions. • The initial cost is higher.

TABLE 8. GUIDANCE AND CONSIDERATIONS IN RELATION TO ORAL IRON REPLACEMENT

The dose of oral iron depends on patient age, the estimated iron deficit, how quickly it needs to be corrected and side effects.
Doses of 150–200 mg of elemental iron have been recommended for a long time for adults. More recent studies suggest that high doses of oral iron cause a paradoxical decrease in iron absorption due to factors such as elevated plasma hepcidin levels *(Moretti D et al., 2015, Schrier SL, 2015)*. Formulations are available in Spain that provide 40–80 mg of elemental iron, which, when administered once (80 mg) or twice (40 mg/12 h) daily, are equally effective and better tolerated.
Toxicity associated with oral iron is higher in elderly patients and such patients should be treated with lower doses. In a randomised study in hospitalised patients over the age of 80 who had iron deficiency anaemia, doses of 15, 50 or 150 mg of elemental iron were equally effective in raising haemoglobin and ferritin levels, while adverse effects were significantly less common with lower doses *(Rimon et al., 2005)*.
Absorption improves when iron is taken in a moderately acidic medium; it is therefore recommended that iron be taken with ascorbic acid (250–300 mg) or half a glass of orange juice. Some ferric gluconate formulations contain ascorbic acid with 80 mg of elemental iron.
Some food components, such as phosphates, phytates and tannates (which are found in coffee, tea, cocoa and red wine), inhibit iron absorption. Other foodstuffs that impair iron absorption are cereals, dietary fibre, eggs, milk and generally any foods with a high calcium content. Many of these items regularly form part of patients' breakfasts. The summary of product characteristics for most oral iron products therefore recommends taking oral iron at least 1 hour before or 2 hours after eating. However, although the administration of oral iron together with food decreases absorption, it improves tolerance and is one of the strategies used by many doctors in the event of side effects (see below).
Iron is best absorbed as the ferrous (Fe^{++}) salt in a mildly acidic medium. Gastric acidity is helpful and medications that reduce gastric acid (e.g. antacids, histamine receptor blockers, proton pump inhibitors) may impair iron absorption. Other medications that impair oral iron absorption are calcium supplements and certain antibiotics (quinolones, tetracyclines) and therefore oral iron should be taken at least 2 hours before or after these medications.

Enteric-coated or sustained-release capsules are less efficient for oral absorption because iron is released too far distally in the intestinal tract (or not at all).

Response to oral iron therapy can be considered satisfactory when an increase in haemoglobin levels of at least 2 g/dL is observed within 3–4 weeks, which is also associated with an improvement in physical well-being and anaemia-dependent signs and symptoms, including depapillation of the sides of the tongue, which is a good indicator of recovery. Smaller increases in Hb levels result in a slower recovery time, which must be considered especially in patients in whom symptoms of iron deficiency (asthenia, lack of concentration) impair performance at work (presenteeism).

Oral iron therapy may take six to eight weeks in order to fully improve anaemia secondary to gastrointestinal bleeding and as long as six months to replenish iron stores.

Gastrointestinal symptoms associated with taking oral iron are common and include metallic taste, dyspepsia, nausea, vomiting, flatulence, diarrhoea and constipation. Some patients may also be bothered by the dark green or tarry stools (they should be warned if they are to undergo a colonoscopy). As a result of this, compliance with oral iron administration may be low. The severity and impact of these effects has been demonstrated in various systematic reviews and meta-analyses of randomised studies *(Tolkien Z et al., 2015; Cancelo-Hidalgo et al., 2013)* and they are estimated to affect 30–43% of patients, depending on the formulation used. Supplements containing smaller amounts of elemental iron are associated with less gastrointestinal toxicity, especially in elderly patients *(Rimon et al., 2005)*. Other supplements, such as iron protein succinylate or ferrous glycine sulphate, which have an enteric coating that reduces absorption, have fewer adverse effects.

Strategies for reducing side effects and improving tolerability include:

- Limiting the dose (≤80–100 mg of elemental iron per day).
- Dividing the total dose and taking it in two daily doses or increasing the time between doses (e.g. every two days) (anaemia has a slower recovery time).
- Taking iron after dinner (reduces absorption, but improves tolerance).
- Changing the formulation (e.g. from ferrous sulphate to ferrous gluconate) or presentation used (e.g. from tablets to oral solution, which makes it easier to titrate doses).
- Changing to intravenous iron.

TABLE 9. CHARACTERISTICS OF INTRAVENOUS IRONS IN SPAIN

Brand name	Venofer®, Feriv® Iron sucrose	CosmoFer® Iron dextran	Ferinject® Ferric carboxymaltose	Monofer[1]® Iron isomaltoside
Indication	Iron deficiency	Iron deficiency	Iron deficiency	Iron deficiency
Max. iron dose in one INFUSION	200 mg	20 mg/kg of body weight	1,000 mg	20 mg/kg of body weight
DURATION of the MAX. INFUSION DOSE	30 min	4–6 hours	15 min	≤1,000 mg: >15 min >1,000 mg: ≥30 min
Max. iron dose by INJECTION	200 mg (3 times/week)	200 mg (3 times/week)	1,000 mg (once/week)	500 mg (up to 3 times/week)
No. of hosp. visits for adm. 1,000 mg	5	1 by infusion / 5 by injection	1	1 by infusion/ 2 by injection
Use in children/adolescents	Not recommended in children	Yes (≥14 years)	Yes (≥14 years)	Not recommended in children

[1] On 19 July 2017, the Spanish Agency of Medicines and Medical Devices (AEMPS) published the following information (Reference: MUH (FV), 8/2017):

1) The Spanish Pharmacovigilance System has received a large number of reports of suspected serious hypersensitivity reactions associated with the administration of iron isomaltoside (Monofer®).

2) All available data are currently being analysed in detail and, as a precaution, the AEMPS recommends that healthcare professionals do not start any new treatment with this product.

TABLE 10. SPANISH AGENCY OF MEDICINES AND MEDICAL DEVICES (*AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS, AEMPS*) RECOMMENDATIONS FOR THE ADMINISTRATION OF INTRAVENOUS IRON

Intravenous iron preparations should only be used at centres that have immediate access to emergency treatments for hypersensitivity reactions.

The administration of a test dose is not recommended since cases of allergic reactions have been reported in patients who had previously tolerated the product well. The patient should be monitored for at least 30 minutes after administration.

Intravenous iron preparations are contraindicated in patients who are hypersensitive to any of the components of the medication and should not be used in patients who have suffered severe hypersensitivity reactions to a different preparation.

Special care should be taken in patients with known allergies to other medications or with immune or inflammatory diseases, such as patients with a history of asthma or eczema or atopic patients.

These preparations should only be used during pregnancy if they are clearly necessary and their use should be restricted during the second and third trimesters in order to protect the fetus as much as possible from potential adverse effects.

Finally, it is important to remember to report all suspected adverse reactions to the corresponding Autonomous Pharmacovigilance Centre or via the website https://www.notificaram.es.

FIGURE 1. FACTORS INFLUENCING THE DECISION TO GIVE TRANSFUSIONS: HOW MUCH AND TO WHOM

NATURE, SOURCE AND ACTIVITY OF BLEEDING

Bleeding due to gastro-oesophageal varices: > risk of rebleeding after overexpansion of blood volume

EXTENT OF BLEEDING

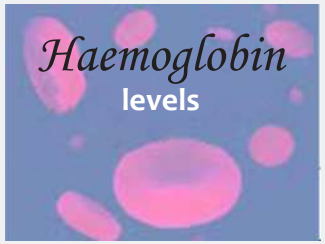
Impact of bleeding on haemodynamic stability: dyspnoea, precordial pain, tachycardia, hypotension

LIKELIHOOD OF REBLEEDING

Jet arterial bleeding, visible vessel observed during endoscopic examination

Restrictive
Hb <7 g/dL

Liberal
Hb <9 g/dL



COMORBIDITIES THAT INCREASE THE RISK OF SEVERE BLEEDING

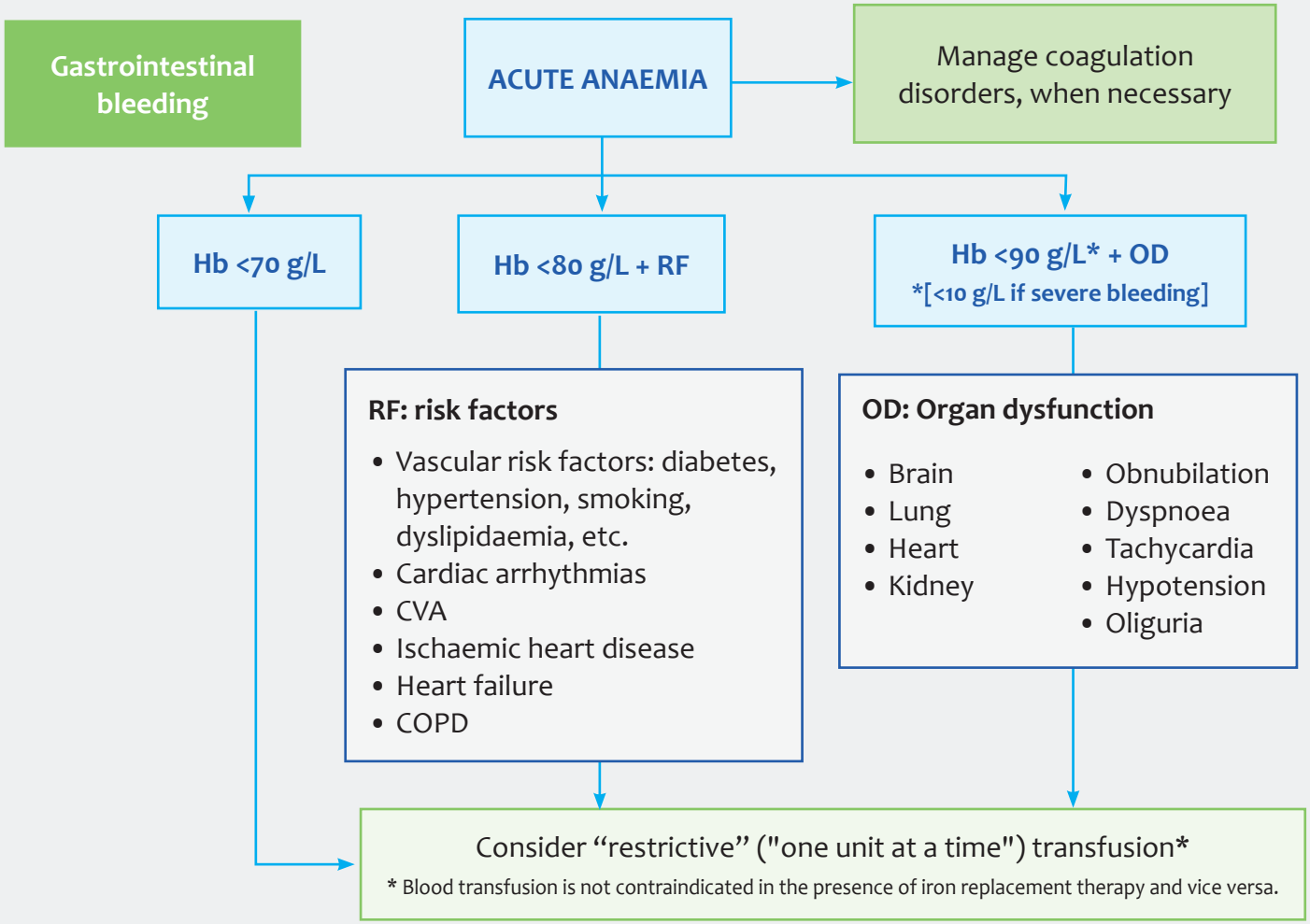
Anticoagulation, taking antiplatelet drugs

COMORBIDITIES THAT INCREASE THE RISK OF TISSUE HYPOXIA,

THEREBY INCREASING THE RISK OF MORBIDITY AND MORTALITY

Concurrent vascular risk factors (diabetes, hypertension, smoking, dyslipidaemia), ischaemic heart disease, heart failure, COPD, CVA, organ dysfunction: brain, lung, heart, liver, kidney

FIGURE 2. INDICATIONS FOR GIVING RED BLOOD CELL TRANSFUSIONS FOLLOWING AN EPISODE OF ACUTE GASTROINTESTINAL BLEEDING



While bleeding is still active, maintaining Hb >70 g/L and around 80 g/L is recommended.

In patients with a history of cardiopulmonary disease, maintaining Hb >80 g/L and around 90 g/L is suggested.

Other factors that have an impact on the transfusion threshold:

Anticoagulants (including discontinuation of treatment, if applicable).

Risk of rebleeding: active bleeding at the time of endoscopy, visible vessel.

FIGURE 3. ALGORITHM FOR THE MANAGEMENT OF CHRONIC ANAEMIA ASSOCIATED WITH GI BLOOD LOSS

RF: risk factors

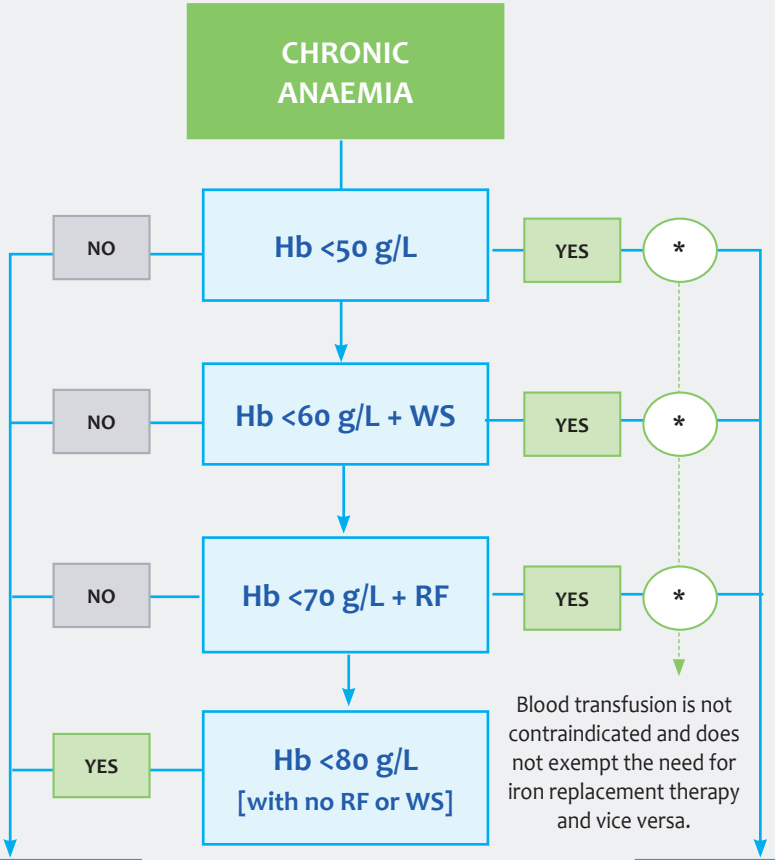
- Vascular risk factors: diabetes, hypertension, smoking, dyslipidaemia, etc.
- Cardiac arrhythmias
- Stroke
- Ischaemic heart disease
- Chronic heart failure
- COPD

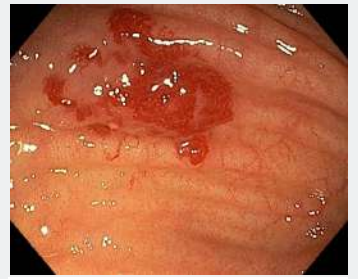
WS: warning signs

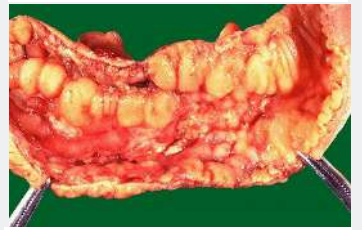
- Tachycardia
- Hypotension
- Dyspnoea
- Angina
- Hypoxia

- Intolerance to oral iron
- Malabsorption
- Refractoriness due to any other cause
- Associated inflammatory condition (see text)
- Kidney failure requiring EPO
- Significant asthenia (which makes it difficult to go back to work, for example)

Consider i.v. iron if:




Angiodysplasia


Crohn's disease

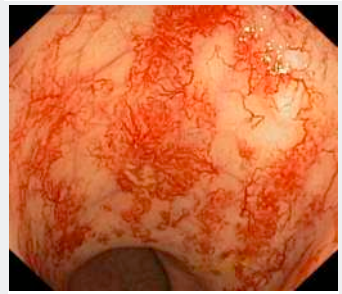
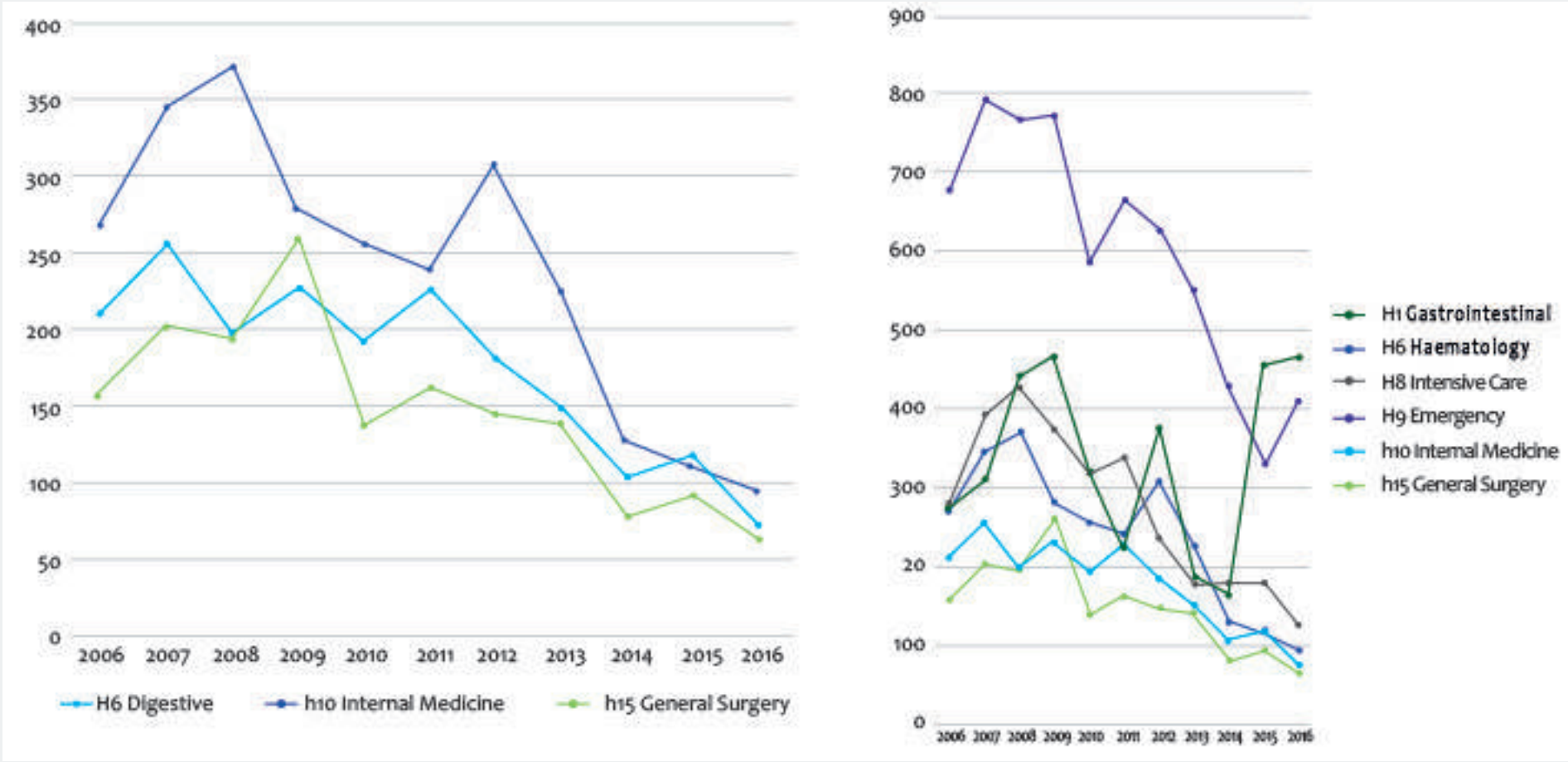
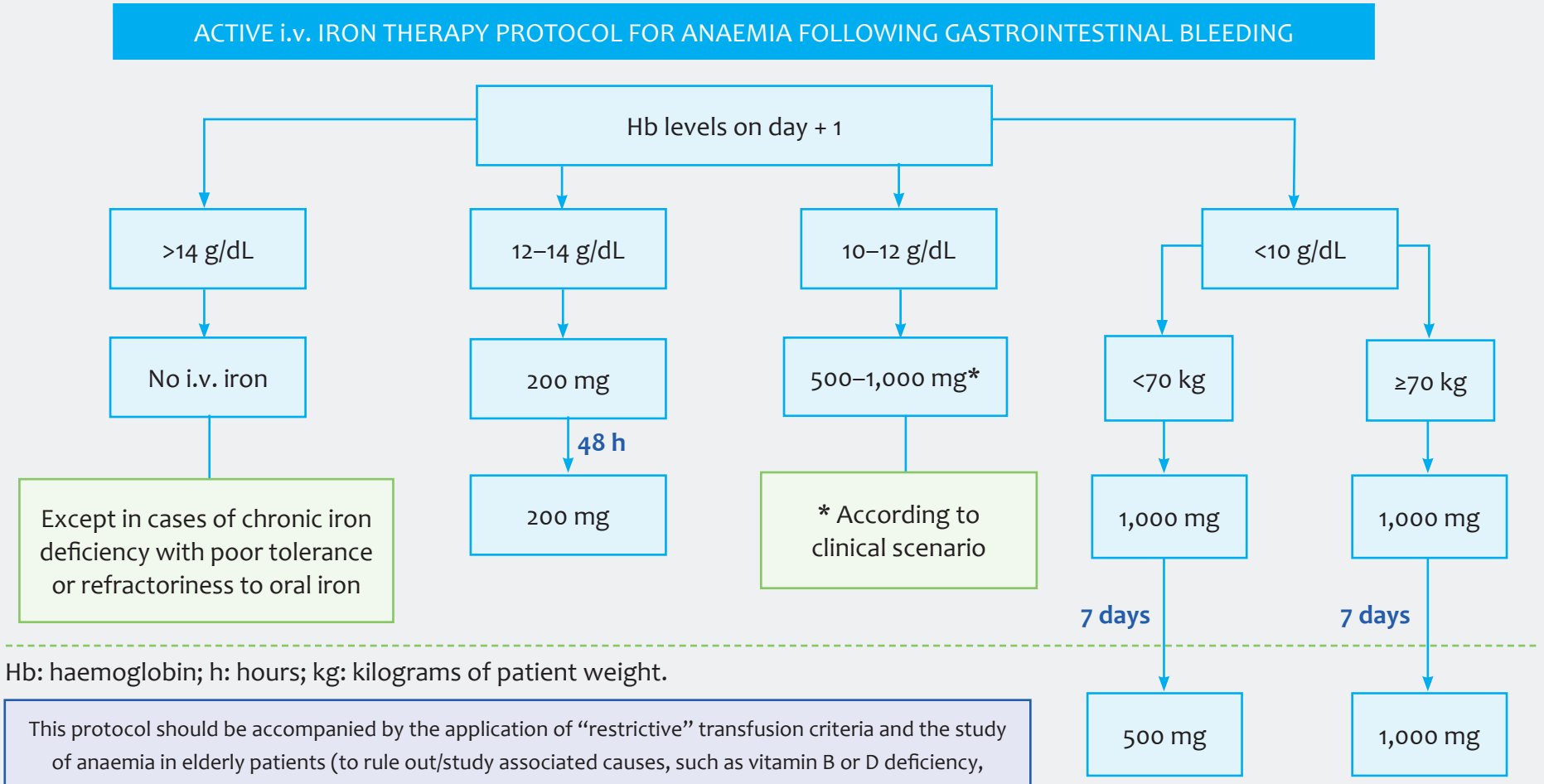

Radiation proctitis

FIGURE 4. NUMBER OF UNITS OF RED BLOOD CELLS UNITS USED AT HOSPITAL SAN JORGE IN HUESCA (2006–2016)



Evolution in consumption of red blood cell concentrates by different services at San Jorge General Hospital (Huesca) (2006–2016). García Erce JA, Transfusion Unit of the Haematology and Haemotherapy Department at HSJ (unpublished observations).

FIGURE 5. DOSAGE OF INTRAVENOUS IRON ACCORDING TO HAEMOGLOBIN (Hb) LEVELS [g/dL]



Hb: haemoglobin; h: hours; kg: kilograms of patient weight.

This protocol should be accompanied by the application of "restrictive" transfusion criteria and the study of anaemia in elderly patients (to rule out/study associated causes, such as vitamin B or D deficiency, chronic kidney disease, hypothyroidism and associated inflammatory components.

One unit of red blood cells provides a quantity of iron equivalent to the quantity provided by 200 mg of intravenous iron.

Necessary resources

[The minimum resources required to implement the protocol are summarised below].

- Site
- Personnel
- Clinical-diagnostic material
- Economic resources
- Support from other levels of healthcare

The aim of this protocol is to guide healthcare and to structure diagnostic and therapeutic decision-making in routine clinical practice; it can therefore be adapted to the specific resources available at each centre. If data are recorded, the inclusion of such data in REDcap-AEG will be assessed.

SITE

Limited to hospitals under the safety conditions indicated in the protocol (see sections relating to management of adverse effects, location of the patient and nursing actions).

PERSONNEL

The multidisciplinary nature of the protocol may result in the involvement of staff from various specialties.

- Haematology Department and Transfusion Unit
- Doctors from the Emergency department
- Gastrointestinal tract and Internal Medicine consultants
- General and Gastrointestinal Surgery consultants
- Intensive Care doctors
- Anaesthesiology and Resuscitation Department
- Clinical Biochemistry Laboratory
- Hospital Pharmacy
- Nurses from the Day Clinic

CLINICAL-DIAGNOSTIC MATERIAL

Application of this protocol requires:

- Ordinary lab material to perform basic blood count, clotting and biochemistry tests
- Blood bank
- Infrastructure for emergency gastrointestinal endoscopies for diagnostic and therapeutic purposes
- Imaging and Radiodiagnostics Department that is able to perform CT angiograms in the event of haemodynamically unstable patients who are difficult to control

- Emergency operating room
- Conventional hospital wards and Day Clinic
- Hospital Pharmacy

ECONOMIC RESOURCES

The protocol does not involve the use of specific economic resources, except for those assigned to the Services or Departments of a hospital designed to provide care to patients with acute gastrointestinal bleeding.

SUPPORT FROM OTHER LEVELS OF HEALTHCARE

Initial healthcare for a patient with gastrointestinal bleeding is given at any hospital belonging to the national healthcare system, which usually has the necessary means and resources to guarantee a quality and safety-focused transfusion policy. It is important to ensure good coordination with the Haematology and Haemotherapy Department and the Transfusion Unit, which should enforce good clinical practice based on the PBM (Patient Blood Management) strategy and supported by restrictive or oligovolemic allogeneic blood transfusion models. It is also important to have massive transfusion protocols in cases of exsanguination, which involve anaesthetists and intensive care doctors especially trained in resuscitation techniques and familiar with the control and management of serious clotting disorders, and also endoscopists, interventional radiologists and surgeons trained in the use of therapies specifically aimed at controlling and stopping bleeding.

ORGANISATION AND OPERATION

The guidelines outlined in this protocol are aimed at making decision-making easier for healthcare professionals who treat any kind of gastrointestinal bleeding cases. While respecting the idiosyncrasy of each centre, it is advisable that both the diagnostic and therapeutic healthcare process is coordinated by the Gastrointestinal Tract specialist (doctor specialising in general internal medicine, doctor in the hospital's emergency department, intensive care doctor or surgeon, as applicable) who is ultimately responsible for assessing all the variables that help determine when, how and who to give transfusions to, with the support and advice of the haematologist. Decision-making will often not be easy **(Figure 1)**.

Recording system

The protocol is open to the possibility of cases being recorded in the REDcap-AEG, which allows different aspects of such cases to be examined at a later stage and prospective studies to be designed aimed at improving the level of evidence and the quality of recommendations for allogeneic blood transfusions and/or intravenous iron in patients suffering from blood loss.

Protocol evaluation

Hospitals that adhere to the protocol will be able to evaluate their degree of compliance by examining suitable indicators, especially

in those cases where variables can be recorded prospectively using applicable software tools. The Haematology Department is responsible for ensuring and controlling rational use of allogeneic blood transfusions within the terms set out in this protocol. The Hospital Pharmacy will offer support and advice in all areas associated with i.v. iron infusion according to the specifications given in the summary of product characteristics for the different formulations used, and ultimately the weighted clinical judgement of the doctor responsible for managing a specific patient should prevail.

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Abbreviations

- ABT: Allogeneic Blood Transfusion.
- AEMPS: Spanish Agency of Medicines and Medical Devices
- AP: Antiplatelet Drugs.
- BP: Blood Pressure.
- BUN: Blood Urea Nitrogen.
- CRP: C-Reactive Protein.
- FFP: Fresh Frozen Plasma.
- GvHD: Graft-versus-host disease.
- Hb: Haemoglobin.
- HR: Heart Rate.
- ID: Iron Deficiency.
- IDA: Iron Deficiency Anaemia.
- LDH: Lactate Dehydrogenase.
- LGIB: Lower Gastrointestinal Bleeding.
- LVEF: Left Ventricular Ejection Fraction.
- MCH: Mean Corpuscular Haemoglobin.
- MCV: Mean Corpuscular Volume.
- OD: Organ Dysfunction.
- PBM: Patient Blood Management.
- RDW: Red Cell Distribution Width.
- rMCH: Reticulocyte Haemoglobin Content.
- sTfR: Soluble Transferrin Receptor.
- TACO: Transfusion-Associated Circulatory Overload.
- TRALI: Transfusion-Related Acute Lung Injury.
- TRIM: Transfusion-Related Immunomodulation.
- TS: Transferrin Saturation.
- UGIB: Upper Gastrointestinal Bleeding.
- WS: Warning Signs.